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Neuropsychological functioning across the ALS disease course and its assessment

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For my husband, Dave, who keeps things silly

Declaration

I declare that the thesis has been composed by myself and that the work has not be submitted for any other degree or professional qualification. I confirm that the work submitted is my own, except where work which has formed part of jointly-authored publications has been included. My contribution and those of the other authors to this work have been explicitly indicated below. I confirm that appropriate credit has been given within this thesis where reference has been made to the work of others.

The work presented in Chapter 1 was partially used for publication in a book chapter titled *'Cognitive and behavioural dysfunction in ALS and its assessment'* in the edited book *'Understanding and Optimizing Quality of Life and Psychological Well-Being'* (Pagnini, F., & Zachary, S. Eds.): ISBN: 9780198757726. The book chapter is authored by Professor Sharon Abrahams (supervisor) and **Mr Christopher Crockford**. Information presented in the thesis chapter was written solely by **Mr Christopher Crockford**.

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included in the present chapter. Dr Ratko Radakovic provided secondary inter-rater reliability data for this study. Professors Ammar AL-Chalabi, Orla Hardiman, and Sharon Abrahams contributed to supervision and intellectual content. The article was published under open access licencing (CC-BY).

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Date:

Signed: Christopher Crockford

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Abstract

Amyotrophic Lateral Sclerosis (ALS) is a rapid and fatal neurodegenerative disease marked by progressive muscle weakness and wasting. Approximately 50% of people with ALS experience changes in cognition and behaviour. Previous research has been mixed as to whether cognition declines over the course of ALS, or whether it is related to proxies of disease progression (e.g., functional disability scales). However, this research has suffered from limitations including the use of inappropriate measures of cognition, imprecise measures of disease progression, high attrition, practice effects, and biased analytic approaches. Fortunately, recent advances in clinical assessment have provided accurate measures of neuropsychological functioning and disease progression, namely, the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) and the King's Clinical Disease Staging.

The present study aims to utilise recent advances in ALS disease metrics to overcome previous limitations and explore the evolution of cognitive and behavioural dysfunction over the course of ALS. Specifically, the aims of the present project are to 1) develop alternate forms of the ECAS to accommodate repeated longitudinal assessment; 2) examine how cognition and behaviour relate to clinical disease stages in ALS; 3) evaluate how cognitive and behavioural symptoms evolve over the course of the disease in ALS; and 4) explore clinicians' attitudes toward cognitive and behavioural screening in ALS.

To achieve Aim 1, two new versions of the ECAS (ECAS-B and ECAS-C) were developed and administered to a group of age, education, and gender matched controls to that of the original ECAS-A validation study. Results demonstrate that the alternate forms of the ECAS (B and C) were equivalent to

the original ECAS-A, reducing practice effects and possessing excellent inter-rater reliability. The ECAS forms were administered longitudinally to a separate group of healthy controls. Over an interval of 4 months, the ECAS-A-B-C showed no evidence of practice effects and excellent test-retest reliability validating their utility in the longitudinal monitoring of cognition in ALS.

The ECAS forms were then used in an international multi-centre clinical sample of 161 ALS patients and 80 matched controls to achieve Aim 2. Patients were grouped into their King's Clinical Disease Stage at time of testing. Analysis revealed a significant cross-sectional relationship between disease stage and ALS-Specific cognitive functions, driven by a decline in verbal fluency performance. A significant relationship was also observed between disease stage and behavioural features. By end-stage disease 80% of patients demonstrated neuropsychological impairment.

Participants were followed up longitudinally to explore the progression of cognitive and behavioural symptoms. Latent Growth Curve models of the ECAS subdomains (utilising the alternate versions) demonstrated a significant decline in ALS Specific cognitive, but not behavioural, functioning over time. This decline was explained by advancing disease stage, the presence of the C9orf72 repeat expansion, and years of education. Rate of change in ALS Non-Specific functions was dependent on baseline performance. Visuospatial functions and perseveration declined at similar rates and were distinct from language, fluency, apathy, and disinhibited behaviour. Cluster analysis of patients revealed a three-cluster solution with one group demonstrating no significant decline, a second group with mild cognitive and behavioural decline, and a third group with more severe neuropsychological decline. When data was restructured by diseases

stage, rather than time, longitudinal results were similar to cross-sectional findings.

To examine clinician's attitudes to cognitive and behavioural screening. Fourteen Health Care Professionals (HCP) working in ALS (Neurologists, Psychologists, and Clinical Care Specialists) were interviewed. Thematic analysis revealed that HCPs recognised the importance of cognitive and behavioural screening in ALS, but that it is not common practice. Important barriers to screening were reported including other members of staff, a lack of resources, and issues concerning patients and their families. Participants suggested increasing training and psychology input, and making screening a standardised protocol to all patients may alleviate these barriers.

Cognition and behaviour are critically related to advancing disease stage, both cross-sectionally and longitudinally. Declining cognitive and behavioural symptoms has important implications for clinical practice, caregiver impact, and end-of-life decision making. However, clinicians report that cognitive and behavioural screening is not common practice and that significant barriers exist. The newly developed alternate forms of the ECAS provide an accurate, effective, and clinically useful means of monitoring cognitive function over the course of the disease in ALS.

Lay summary

Amyotrophic Lateral Sclerosis (ALS) is a rapid and fatal neurological disease. Approximately half of patients will experience changes in the way they think and behave. Some researchers have attempted to examine if these changes worsen as the disease progresses, with mixed results. However, this research has been limited by inaccurate research methods. These limitations include the use of tests that require intact motor speed, which is compromised in ALS. Practice effects are improvements in test performance due to familiarity with the test which may mask a decline and have not been accounted for previously. Furthermore, methods of measuring disease progression are highly variable between individuals. The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was recently developed to overcome motor speed limitations in ALS, while the King's Clinical Disease Staging was proposed as an accurate and standard measure of disease progression. The aim of this research was to further develop the ECAS to overcome practice effects and explore how thinking and behaviour changes evolve over the course of the disease in ALS. Finally, clinicians working in ALS will be interviewed regarding current attitudes and practices toward the assessment of thinking and behaviour changes.

Two alternate forms of the ECAS were developed to overcome practice effects. The new forms (ECAS-B and ECAS-C) were designed. The new ECAS forms were administered to a group of healthy adults who match the profile of ALS patients. Performance on the ECAS-B and ECAS-C was equivalent to the ECAS-A demonstrating that the new forms retain the same properties and level of difficulty as the original ECAS-A. When the ECAS-A was given to a different group of healthy adults over time, an improvement in scores was observed.

However, when the new forms (B and C) were given to healthy adults over time, no improvement in performance was observed. Finally, the new ECAS forms were given to a separate group of healthy adults to determine normal variation over time, so that cut-off scores of abnormal change over time can be determined. The evidence from this research suggests that the new ECAS forms provide an accurate way of measuring thinking abilities over time and provide a means of overcoming limitations with previous research.

These new ECAS forms were then administered to a group of people with ALS, recruited from Dublin, Edinburgh, and London. A group of healthy adults, matched by age, gender, and education were also recruited. Patients with ALS were divided into groups based on their King's Clinical Disease Stage and their ECAS scores were compared. Results demonstrate that people in more advanced disease stages showed worse thinking abilities and behaviour, such that by late-stage disease 80% of people were impaired. This group of patients and healthy adults were followed up four times every four months to examine how their thinking and behaviour changes over the disease course. Results here demonstrate that thinking abilities decline with time. Thinking abilities and behaviour were related to advancing disease stage, years of education, and the presence of a gene (C9orf72) which forms a genetic overlap between ALS and dementia.

Clinicians working in ALS were interviewed and they reported that assessment of thinking and behaviour is important, but not common. Significant barriers to assessment were reported including other members of staff, a lack of resources, and issues concerning patients and their families. Participants

suggested increasing training and psychology input and making assessment standard to all patients.

This study demonstrated that thinking and behaviour does indeed worsen across the disease course. This finding is important for patients, their families, and clinicians due to the important decisions and care that is required in ALS as the disease advances. However, clinicians' report that assessment of thinking and behaviour may not occur as often as it should due to important barriers. The new ECAS forms provides a means for clinicians to monitor patients' thinking and behaviour throughout their disease.

CHAPTER 1: Introduction and background

Cognitive and behavioural symptoms are now recognised as common features of amyotrophic lateral sclerosis (ALS). Where historically these functions were thought to be spared, it is now well documented that:

- A significant proportion of people with ALS experience severe changes in behaviour and personality, presenting as frontotemporal dementia (FTD).
- In addition to this, a larger proportion will experience milder cognitive and behavioural changes detectable through neuropsychological assessment.
- The remaining patients with ALS will demonstrate no significant alteration in cognition or behaviour, and present with motor system involvement only.

This chapter will begin with a description of ALS and introduce the concept of disease staging, important for tracking the progression of the disease. Following this, cognitive and behavioural symptoms in ALS will be explored, in addition to the methods currently available in assessing such symptoms.

1.1. What is ALS?

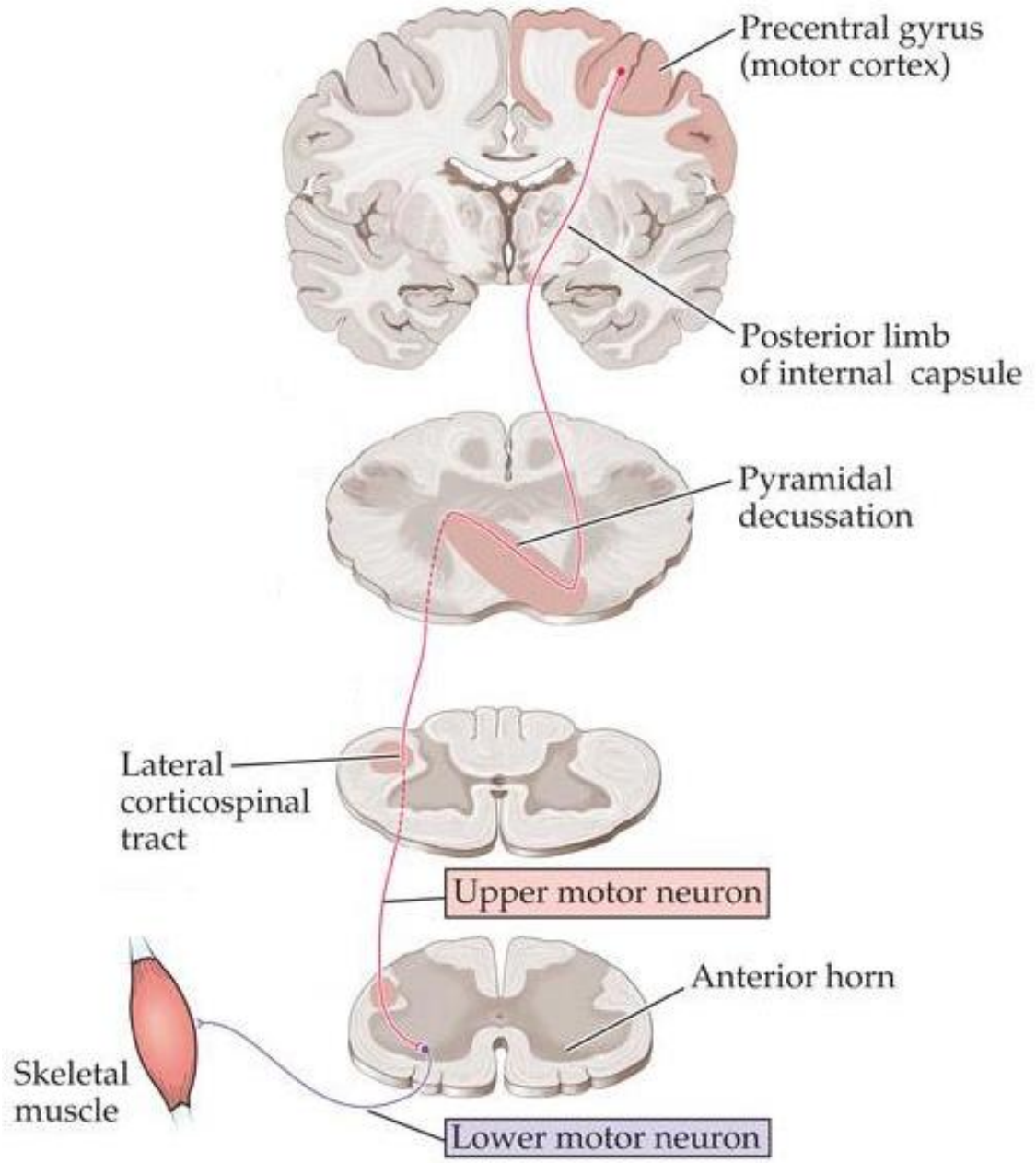
Motor Neuron Disease (MND) describes a group of conditions marked by degeneration of upper (UMN) and/or lower motor neurons (LMN) of the brain and spinal cord. MND is a progressive and fatal neurodegenerative condition that not

only affects voluntary and autonomic movement, but also areas of the brain responsible for cognitive functioning and behaviour. Originating in the motor cortex, UMNs form synapses with LMNs in the motor nuclei of the brainstem and spinal cord (Kiernan et al. 2011; Figure 1.1). LMNs are required by the autonomic and voluntary nervous system to innervate muscle groups responsible for movement, including breathing, swallowing, and communication. Degeneration of the motor neurons interrupts this innervation, and over time, the muscles fatigue, weaken, and eventually paralyse (Kiernan et al. 2011). Degeneration of LMNs result in weakness, atrophy, and fasciculations, whereas degeneration of the UMNs results in weakness, brisk reflexes, and muscle stiffness. Under the umbrella of MND, there are several disease subtypes characterised by differential involvement of UMNs, LMNs, or both. Primary Lateral Sclerosis (PLS) presents with UMN signs only, such as spasticity of limbs, and brief reflexes, while Progressive Muscular Atrophy (PMA) predominantly affects the lower motor neurons causing muscle weakness. Amyotrophic Lateral Sclerosis (ALS) is the most common form of MND, with clear clinical signs of both UMN and LMN involvement (Elman et al. 2008).

Approximately 80% of those with ALS will present with initial symptoms in the limbs (degeneration of motor neurones descending into and from the spine) and may go on to develop bulbar symptoms (progressive bulbar palsy for degeneration of the LMNs and pseudobulbar palsy for degeneration of the UMNs) as the disease progresses. Similarly, patients presenting with symptoms in bulbar muscles (degeneration of motor neurones descending into and from the brainstem) often go on to develop symptoms in the limbs (Kühnlein et al., 2008). ALS is a rapidly progressive disease compared to phenotypic variants PMA and

PLS with a median survival of 2 to 3 years from symptom onset and death usually due to respiratory failure (Al-Chalabi & Hardiman, 2013). ALS affects more men than women, with a ratio of approximately 1:1.4, the incidence of which is 2.2 per 100,000 for women and 3.1 for men (Logroscino et al. 2010).

Figure 1.1. Corticospinal tract pathway



Source: Pearson Education (2009)

1.2. Genetics of ALS

Cases of ALS are classified as sporadic, accounting for 90-95%, or familial, accounting for the remaining 5-10% (Al-Chalabi et al., 2016; Byrne at al. 2011). Most genes associated with ALS are autosomal dominant, with over 20 being identified to date (Hardiman, Kiernan, & van den Berg, 2016). Of the approximately 10% of ALS cases where a genetic contribution can be identified, the most common finding is C9orf72 hexanucleotide repeat expansion, followed by superoxide dismuatase (*SOD1)* mutations, transactive response DNA binding protein 43 (TDP-43), and Fused in Sarcoma (FUS) (Chiò et al., 2008). C9orf72 accounts for up to 50% of familial cases and 8% of sporadic ALS cases (De Jesus-Hernandez et al., 2011; Hardiman et al., 2016; Majounie et al., 2012). The presence of the C9orf72 mutation is associated with worse prognosis, possibly driven by spinal-onset males (Rooney et al., 2016a) and is population dependent, demonstrating significant geographic variability (Majounie et al., 2012; Sabatelli et al., 2012; van der Zee et al., 2013). Mutations in *SOD1* account for approximately 15% of familial and 5% of sporadic cases of ALS. Mutations in DNA/RNA binding proteins, TDP-43 and FUS account for 10-15% of familial ALS. Most recently, NIMA (never in mitosis gene-A)-related kinase 1 (NEK1) variants have been associated with ALS, accounting for an additional 3% of cases (Kenna et al., 2016).

1.3. Diagnosing ALS

Definitive diagnostic tests for ALS are lacking. Presently, diagnosis is based on clinical and electromyographic results, and the exclusion of mimics. Elecromyography (nerve conduction analysis) is useful in detecting LMN signs,

however, measurements of UMN involvement is more difficult. Patients with LMN disease (PMA) often go on to develop UMN signs later in the disease. Similarly, some patients who present with UMN signs (PLS), go on to develop LMN signs later in the disease (Ince et al., 2003; Gordon et al., 2006a; Tartaglia, et al., 2007). This may therefore cause diagnostic confusion between PMA, PLS, and ALS such that some authors question whether these conditions represent discrete phenotypes or a single disease continuum (Al-Chalabi et al., 2016). Nevertheless, ALS represents the majority of cases of MND in which both the UMN and LMN are involved.

The El-Escorial diagnostic criteria were developed to facilitate the inclusion of ALS in clinical trials. The El-Escorial criteria (Brooks, 1994) and its revision (Brooks, Miller, Swash, & Munsat, 2000) propose a diagnosis of ALS based on the presence of LMN degeneration (by clinical, electrophysiological, or neuropathological examination), evidence of UMN degeneration (by clinical examination), and the progressive spread of symptoms or signs (within a particular region or to other regions). Additionally, there must be an absence of evidence of other disease processes that might explain the presence of UMN and LMN symptoms. Regarding diagnostic certainty, the El-Escorial criteria apply diagnoses under definite, probable, possible, and suspected ALS labels. The revised criteria (Airlie House Criteria) removed suspected ALS, and included laboratory supported probable ALS (see Table 1.1).

However, a population-based study on the utility of the El-Escorial criteria and its revision suggested that it is overly restrictive with 10% of patients having possible or suspected ALS at the time of death. Unfortunately, the application of the Airlie House Criteria made no observable impact on the classification of

patients (Traynor et al., 2000). In 2008, a further revision to the criteria was employed, the Awaji-Shima criteria (Carvalho et al., 2008). The Awaji criteria (Table 1.1) modified the Airlie House criteria by allowing the concordant use of clinical and electrophysiological measurements in determining diagnostic certainty. The resulting criteria improved diagnostic sensitivity, particularly for bulbar onset patients (Carvalho & Swash, 2009). The improvement in diagnostic certainty has been externally validated (Boekestein et al., 2010; Geevasinga et al., 2016) with an improvement of 23% of patients being classified as having probable or definite ALS (Costa, Swash, & de Carvalho, 2012a). However, the El-Escorial criteria and its revisions were developed for the use in clinical trials and authors have questioned its clinical utility and its representation of the heterogeneity of ALS (Agosta et al., 2015; Rutter-Locher et al., 2016). Recently, it has been argued that the category of

Table 1.1. Criteria for diagnostic certainty for ALS

Clinical Certainty	Signs
El-Escorial Criteria (1994)	
Definite ALS	UMN and LMN signs in three regions
Probable ALS	UMN and LMN signs in two regions with UMN signs rostral to LMN signs
Possible ALS	UMN and LMN signs in one region, UMN signs in two+ regions, LMN signs rostral to UMN signs
Suspected ALS	LMN signs is two+ regions
Airlie House Revision (2000)	
Clinically Definite ALS	UMN and LMN clinical signs in three regions
Clinically Probable ALS	UMN and LMN clinical signs in two regions with UMN signs rostral to LMN signs
Clinically Probable ALS - Laboratory supported	UMN and LMN clinical signs in one region, or UMN signs in one region with LMN signs by EMG in 2+ limbs (with proper exclusion of other causes)
Clinically Possible ALS	UMN and LMN clinical signs in one region, UMN clinical signs in 2+ regions, LMN signs rostral to UMN signs, where clinically probably ALS laboratory supported cannot be shown
Awaji-Shima Revision (2008)	
Clinically Definite ALS	UMN and LMN clinical or electrophysiological signs in the bulbar regions and at least two spinal regions, or UMN and LMN signs in three regions
Clinically Probable ALS	UMN and LMN clinical or electrophysiological signs in two regions with UMN signs rostral to LMN signs
Clinically Possible ALS	UMN and LMN clinical electrophysiological signs in one region, UMN signs in 2+ regions, LMN signs rostral to UMN signs

possible ALS is sufficient for diagnosis. This is in part due to observations that clinical trials which included the category of possible ALS found a negligible number of patients receiving the wrong diagnosis. Additionally, it has been

recommended that the categories of probable and definite ALS be replaced with appropriate and validated disease staging systems, which includes appropriate imaging techniques, cognitive impairment, concomitant signs such as sensory and oculomotor disturbances, non-ALS phenotypes such as PLS, and genetics (Ludolph et al., 2015). However, these recommendations have yet to be validated (Strong et al., 2017).

1.4. Disease progression and staging

Understanding disease progression is important for both research and clinical practice. It aids description of the natural history of the disease and gain understanding of progression patterns, informs prognosis, and provides information as to the efficacy and effectiveness of clinical trials. Disease spread through the ALS nervous system has been suggested to occur contiguously and caudally, through adjacent areas in upper and lower motor neurons (Bak & Chandran, 2012). For example, individuals whose disease begins in the bulbar region are more likely to develop spinal involvement than vice versa. Spread may be due to motor neuron susceptibility, for example, motor neuron size, axon length, or microenvironment (Ravits & La Spada, 2009). As such, disease progression often presents as the worsening involvement within a region, and to other regions of the body. The resulting degeneration expresses as declining functional ability. Muscle strength tests, pulmonary function tests, and electrophysiological measures (including the recent Motor Unit Number Index) are methods of recording physical disease progression in ALS (Rutkove, 2015). However, clinically, the ALS Functional Rating Scale (ALSFRS) is commonly used as a measure of disease progression (ALSFRS, 1996).

1.4.1. The ALSFRS and MITOS Disease staging systems

The ALSFRS is a measurement of physical function in activities of daily living in ALS, covering bulbar functions, gross motor tasks, and fine motor tasks. The ALSFRS was revised (Cedarbaum et al., 1999) to incorporate respiratory function (ALSFRS-R). Disease progression on the ALSFRS-R has been shown to be curvilinear in that rate of functional decline is more rapid in early and late phases of the disease. The initial decline slows after 18 months of symptom onset and declines more quickly in patients with bulbar onset (Gordon & Cheung, 2006b; Gordon et al., 2010a). While the curvilinear form of ALSFRS-R progression is important, on a case-by-case basis, the ALSFRS-R may not be linear or curvilinear. Factors such as age and site of onset have modifying influences on the predictive ability of the ALSFRS-R and introduce large degrees of variability resulting in a heterogeneous profile of decline (Mandrioli et al., 2015; Swinnen & Robberecht, 2014).

The prognostic value of the ALSFRS-R has been improved by the amalgamation of symptom duration making disease severity a function of time (Gordon & Cheung, 2006b; Kimura et al., 2006; Labra et al., 2015). The equation, which calculates the average loss of function per month of disease duration, is as follows:

$$Progression\ Rate = \frac{48(max\ score) - (ALSFRS\ score\ at\ visit)}{symptom\ duration\ at\ visit}$$

In a further attempt to improve prognostic value of the ALSFRS-R, this ALSFRS-R slope has been incorporated into a simple algorithm with site of onset and the presence or absence of executive dysfunction (Elamin et al., 2015). However, the unitary construct of the ALSFRS-R score may not be meaningful and rather, the ALSFRS-R has greater utility when viewed multidimensionally. In their factor analysis, Franchignoni, Mora, Giordano, Volanti, and Chiò (2013) report three dimensions of the ALSFRS-R: bulbar, fine and gross motor function, and respiratory function. This has been recently validated in an Irish cohort (Rooney, Burke, Vajda, Heverin, & Hardiman, 2016b).

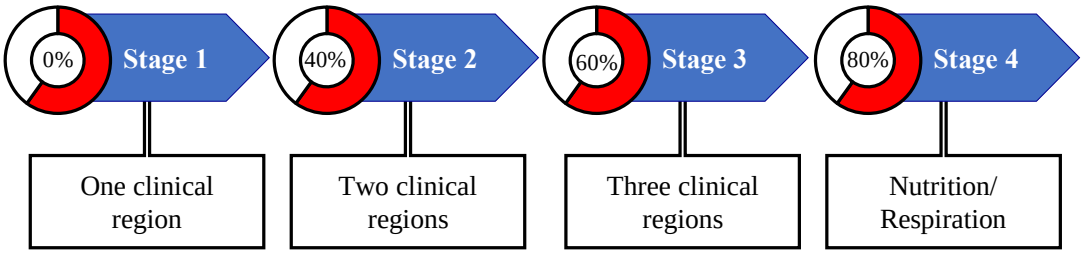
In addition to using the raw scores to measure disease progression, the ALSFRS-R has been adapted into a functional staging system. The ALS Milan Torino Staging (MITOS) system is based on the loss of independent functioning in domains present in the ALSFRS-R (Chiò, Hammond, Mora, Bonito, & Filippini, 2015). The number of domains lost constitute the disease stage ranging from 0-4, with Stage 5 constituting death. The domains are: self-care/walking, swallowing, communication, and breathing. As such, the MITOS system is a functional staging system reflecting the progressive disability associated with ALS, and advancing disease stages are shown to correlate with lower quality of life (Chiò et al., 2015). In a study to validate the utility of the MITOS in predicting long-term survival, Tramacere et al., (2015) found the MITOS to have good predictive sensitivity to death or respiratory failure longitudinally (82% and 71% at 12 and 18 months). However, the specificity of the MITOS was less accurate at 63% and 68% (respectively) suggesting the system overestimates progression in some individuals. Further issues exist with the MITOS system include its skew to late-stage disease in which ALS patients tend to stay at Stage 0 (which

purportedly indicate no loss of function) until the disease has progressed quite significantly. The complete loss of independent function in a region is a milestone that people with ALS may never reach despite the presence of involvement in multiple bodily regions. For example, it is feasible for an individual to have physical involvement of the bulbar region, in addition upper and lower limb involvement but still be in MITOS Stage 0.

1.4.2. The King's Clinical Staging system

An important advancement in developing measures of disease progression was the publication of the King's Clinical Staging System (Roche et al., 2012). The stages of the King's system are based on the number of bodily regions involved by clinical examination, and can be estimated from ALSFRS-R scores with an intra-class correlation coefficient of .92 (Balendra et al., 2014). Stage 1 is defined as the presence of one bodily regions (e.g., upper limbs), Stage 2 is defined by the presence of two bodily regions (e.g., upper limbs and lower limbs), Stage 3 is defined by the presence of three bodily regions (i.e., upper limbs, lower limbs, and bulbar region). Stage 4 of the King's system is reached when the patient meets National Institute for Health and Care Excellence guidelines (NICE, 2016) for respiratory or nutritional intervention (i.e., loss of 10% body weight from baseline; FVC < 50% predicted or < 80% predicted when respiratory symptoms are present; SNIP < 50cmH_2O or < 65cmH_2O for men / < 55cmH_2O for women when symptoms are present; persistent drop of > 10cmH_2O per 3 months on repeated assessment).

Figure 1.2. The King's Clinical Staging System



As displayed in Figure 1.2, the stages of the King's system are shown to have standardised median percentages of disease course with involvement of a second region at ~40%, a third region at ~60%, and Stage 4 at ~80% of the disease course. Diagnosis was found to occur at a similar point as Stage 2. In a large-scale validation study of the utility of the King's system for clinical trials, Balendra et al. (2015) found that the majority of ALS patients progressed to consecutive stages, with the time spent in stages 2-4 (post diagnosis) ranging from 3-7 months. No participant progressed to an earlier stage of the disease, whereas a small number of patients did so using the MITOS system (Chiò et al., 2015). As such, Balendra et al., (2015) suggest that the King's Clinical Staging System may prove useful as predictable and shorter end-points in clinical trials. Imaging research has demonstrated bilateral atrophy of the homunculus which degenerates continuously with functional decline in respective bodily regions (Bede et al., 2013; Schuster et al., 2014) validating the use of clinical features to stage neurological disease progression.

Two studies to date have compared the MITOS and the King's Clinical Staging System. Ferraro et al. (2016) compared the system on 545 incident cases of ALS. Death occurred with increasing probability using the King's staging, such

that 22% of people with ALS in Stage 1 died, 36% in Stage 2, 45% in Stage 3, and 61% in Stage 4. However, no such consistent pattern was observed for the MITOS system where death occurred in 33%, 46%, 68%, 63%, and 64% of patients in Stages 0-4 consecutively. Comparison of the prognostic abilities and linearity of the two systems showed that the King's system had greater homogeneity within stages (differences in survival were smaller within a stage), discriminatory ability (differences in survival between stages), and linearity than the MITOS system. Standardised proportions found in Ferraro et al.'s study were similar to those by Roche et al. (2012). The MITOS, conversely, had standardised proportions of 35%, 67%, 79%, 100%, and 104% of the disease course demonstrating significant skew to late-stage disease. Recently, Fang et al. (2017) found a similar bias in the MITOS to end-stage disease compared to the King's staging. For instance, the King's Stage 3 linked most closely to the MITOS Stage 0 and 1. For King's Stage 4 (i.e., end-stage disease), more patients fell into MITOS Stage 1 and 2. Rather than specifying the King's Clinical Staging System to be superior, Fang et al. suggest the two systems are complimentary with the MITOS system describing loss of function and the Clinical Staging System describing disease spread. As such, the two systems may be combined to describe detailed information, for example, K4M1 describes a patient in end-stage disease (King's Stage 4) but with relative intact functional abilities (MITOS Stage 1). Despite the evidence of clinical and prognostic efficacy of using clinical staging in ALS, disease staging in ALS is not used widely in practice (Rutter-Locher et al., 2016).

1.4.3. Post-Mortem Staging

A final important staging system developed for ALS is that of TDP-43 neuropathological disease stages. TDP-43 is an RNA-binding protein coded by the TARDBP gene, present in almost all ALS cases (Neumann et al., 2006). In a large study of pathological TDP-43 inclusions, Brettschneider et al. (2013) grouped ALS patients into disease stages based on the profile of TDP-43 depositions in the brain. Stage 1 is defined by TDP-43 inclusions in the primary motor cortex, LMNs of the spinal cord (α-motor neurons), and cranial nerves V, VII, and XII (responsible for facial muscles). In Stage 2, the pathology of Stage 1 was evident, with additional primary involvement of the reticular formation of the brainstem. Stage 3 includes the pathology of Stage 2 but with the prefrontal neocortex included. Finally, in Stage 4, TDP-43 pathology extends to the hippocampus. Imaging studies exploring diffusion tensor imaging tract correlates have supported these pathological changes (Kassubek et al., 2014; Schulthess et al., 2016). For example, in a large-scale multi-centre study of 253 ALS and 189 healthy controls, fractional anisotropy using Diffusion Tensor Imaging (DTI) revealed significant changes in white matter tracts in the frontal lobes and the hippocampal regions. When segregated by ALSFRS-R as a proxy of disease progression, patterns of brain alterations followed post-mortem neuropathological TDP-43 deposition patterns (Müller et al., 2016). While these advances may elucidate the pathological progression of ALS in the brain, their clinical utility has yet to be established.

1.5. The ALS-FTD Spectrum

ALS has historically been viewed as a disease affecting the motor system solely, sparing non-motor functions. However, descriptions of non-motor symptoms have been described in ALS for almost as long as the disease itself. Since 1874 when Charcot first described the clinical picture of ALS (Rowland, 2001), depictions of patients with cognitive and behavioural symptoms emerged from the 1880s onward (Bak, 2010). The neglected attention paid to cognitive and behaviour symptoms in ALS can be understood for several reasons, many of which pervade to this day. These include a) cognitive and behavioural assessment tools not suited to motor disability, b) small sample sizes reducing power to detect mild differences or changes, and c) learning effects from repeated assessment masking impairment. While many of these issues continue to complicate measurements of cognition and behaviour, advancements in recent years have allowed for greater precision.

Frontotemporal dementia or frontotemporal lobar degeneration (FTD), are umbrella terms describing degenerative diseases marked by differential and heterogeneous involvement of the frontal and temporal lobes. The prevalence of FTD in the general population is approximately 15-22 per 100,000 (Onyike & Diehl-Schmid, 2013). The most common form of FTD is behavioural variant, the characteristic hallmarks of which include changes in personality, social conduct, and executive functions (Rascovsky et al., 2007; 2011). Semantic dementia is defined by the loss of word meaning and knowledge. Progressive non-fluent aphasia is a language variant of FTD characterised by the loss of words but maintenance of meaning, and speech apraxia (McMonagle & Kertesz, 2016). Semantic dementia and progressive non-fluent aphasia are relatively uncommon

compared to behavioural variant FTD. While a relationship between ALS and FTD, has been suspected as early as 1922 (Nitrini, 2014), contemporary developments in clinical, imaging, genetic, and pathological findings have now established that ALS and FTD share considerable overlap (Goldstein & Abrahams, 2013).

It is estimated that approximately 15% of patients diagnosed with ALS possess the cognitive and behavioural characteristics of FTD, with a further 35% of ALS patients experiencing milder cognitive and behavioural changes. Executive dysfunction and behaviour change (e.g., apathy, eating and stereotypic behaviours) are common in both diseases (e.g., Lillo et al., 2009; 2012a). A similar percentage of FTD patients develop the physical hallmarks of ALS (Lomen-Hoerth, Anderson, & Miller, 2002). A study by Burrell, (2011) found that while 12.5% of patients with FTD also met criteria for MND, an additional 27.3% presented with evidence of milder motor system involvement. A sample of studies examining the prevalence of neuropsychological impairment in ALS are summarized in Table 1.2. Thus, the prevalence of FTD in ALS is approximately 15%, with a further 35% demonstrating milder cognitive and behavioural abnormalities, and the remaining patients presenting with motor-only symptoms.

Structural and functional neuroimaging of ALS has suggested involvement beyond the primary motor cortex to extramotor areas including the frontal and temporal regions (see Chiò et al., 2014 for overview), which are in turn implicated in FTD. Several large studies have demonstrated that involvement of extramotor areas in ALS obeys an overlapping gradient with diagnosis, such that, patients with ALS-FTD show the most widespread involvement, followed by ALS with

milder cognitive and behavioural changes, and finally, ALS with pure motor symptoms.

Table 1.2. Prevalence of neuropsychological impairment and FTD in patients with ALS

Citation	*N*	Cognitive impairment	Behavioural impairment	FTD
Massman et al. (1996)	146	35.6%	-	-
Ringholz et al. (2005)	279	31.9%	-	14.7%
Witgert et al. (2010)*	225	60.3%	24%	-
Phukan et al. (2012)	160	34.1%	-	13.8%
Montusichi et al. (2015)	183	31.2%	6%	12.5%
Murphy et al. (2016)	274	54.2%	14.1%	6.5 - 16.5%

Note. * Did not differentiate FTD and non-FTD cognitive/behavioural impairment. Cognitive impairment refers to non-FTD impairment.

Canosa et al., (2016) examined this gradient using F-FDG-PET. ALS patients with cognitive impairment (compared to ALS patients without cognitive impairment) demonstrated left-dominant clusters of hypometablism in the superior frontal gyrus, anterior cingulate, medial frontal gyrus, and the cingulate gyrus. The same pattern, but more widespread, was observed when ALS patients with cognitive impairment were compared to ALS-FTD patients. Here, ALS-FTD patients demonstrated greater hypometablism in the inferior, middle, and superior frontal gyri. Mioshi et al. (2013) similarly found that ALS with and without cognitive/behavioural impairment, and ALS-FTD showed similar patterns of cortical involvement using voxel-based morphometry. When compared to controls, ALS patients had grey matter atrophy in the temporal and frontal lobes, cerebellum, superior parietal lobes, and the putamen. ALS patients with

cognitive/behavioural impairment demonstrated a similar patter, but with significantly greater grey matter involvement in the superior frontal and superior parietal regions. ALS-FTD patients and ALS with cognitive/behavioural impairment showed overlapping cortical involvement, but with ALS-FTD having more prefrontal and anterior temporal involvement. However, extra-motor atrophy may not be restricted to patients with observable cognitive and behavioural abnormalities. Bede et al. (2013) found that cognitively intact patients also possessed non-motor cortical involvement in the right occipital, left inferior temporal (para-hippocampal), right superior temporal gyrus, and right superior frontal gyrus. Rather, 'neuropsychologically-intact' patients may also have changes that are undetectable by current assessment methods, or have not progressed enough at the time of assessment to be detectable.

Finally, genetically the presence of FTD in ALS (ALS-FTD) has been associated with the presence of the C9orf72 (chromosome 9 open reading frame 72) repeat expansion, observed in approximately 12% of familial FTD cases and 24% of familial ALS cases (Byrne et al., 2011; De Jesus-Hernandez et al., 2011). C9orf72 carriers are reported to have higher rates of cognitive and behavioural impairment, in addition to higher rates of dementia and neuropsychiatric features (Byrne et al., 2012; Hardiman et al., 2016; Snowden et al., 2012). Cortical changes may also be exacerbated by C9orf72 genetic phenotype (Westeneng et al., 2016) and TDP-43 pathology has also been found in almost all ALS cases and over 50% of FTD cases (Neumann et al., 2006).

1.6. Cognition in ALS

Given the demonstrable overlap between ALS and FTD, neuropsychological research has often focused on cognitive abilities thought to be mediated by the frontal and temporal lobes. The prefrontal cortex is thought to contribute to higher-order executive functions such attention, planning, organising, decision making, and social cognition. The temporal lobe, conversely, plays a role in language functions and the formation and retrieval of memory. A summary of the main cognitive research studies in ALS are summarised in Appendix I.

1.6.1. Executive function

Executive functioning describes a broad range of inter-related higher order cognitive abilities that allow individuals to determine goals, formulate ways of achieving those goals, and adapt to changing circumstances to achieve those goals (Burgess & Alderman, 2013). Assessment of executive functioning has been highly variable in ALS due to the use of tests dependent on intact motor functioning, but also due to the interconnectedness of different executive functions. Structures of executive functioning, namely attention, working memory, concept formation, and cognitive flexibility have been examined in ALS.

Attention is perhaps one of the most fundamental aspects of executive functions, allowing an individual to focus, and sustain that focus, on relevant information. Ringholz et al. (2005) has suggested that ALS may be commonly typified by attentional impairments. Assessing attentional abilities can be complicated as tasks usually involve other cognitive processes. However, impairment of selective attention, or an inability to focus on one stimuli in the presence of multiple competing stimuli, has been demonstrated in ALS (Pinkhardt

et al., 2008; Volpato et al., 2016; Witgert et al., 2010). Selective attention has been studied using the Stroop Colour-Word Test, which requires individuals to read as quickly as possible a list of words, each presented in a different colour (see Figure 1.3). In one condition, the congruent condition, the colour names are presented in the congruent colour (e.g., the word 'RED' is presented in the ink colour red). In the incongruent condition, the word is presented in a non-complimentary colour (e.g., the word 'RED' is presented in the ink colour green). Successful completion of the task requires an individual to selectively attend to either the word or the colour, while inhibiting interference of competing stimuli. As such, the Stroop task may also be considered a test of cognitive inhibition.

Figure 1.3. The Stroop task

Congruent:	**RED**	**GREEN**	**BLUE**
Congruent:	**RED**	**GREEN**	**BLUE**
Incongruent:	**RED**	**GREEN**	**BLUE**

While some researchers have found those with ALS make more interference inhibitory errors i.e., failure to inhibit the word name (Christidi, Zalonis, Smyrnis, & Evdokimidis, 2012; Pinkhardt et al., 2008; Zalonis et al., 2012), in studies that controlled for motor speed, this impairment was not found (Abrahams et al., 1997; Stukovnik, Zidar, Podnar, & Repovs, 2010) suggesting potentially intact selective attention/inhibition.

Cognitive inhibition has also been examined using the Hayling Sentence Completion Test. The Hayling test consists of two parts. In part A, participants are asked to complete a series of sentences with a logical response. In part B, participants must inhibit the logical response in favour of an incongruent and unrelated response. In ALS, inhibitory deficits have been observed using the Hayling test (e.g., Carluer et al., 2015; Lillo et al., 2012a), but not consistently (e.g., Girardi, Macpherson, & Abrahams, 2011; Taylor et al., 2013).

In addition to selective attention and inhibition, Pettit et al. (2013) demonstrated deficits in divided attention in patients with ALS. In this study, participants were asked to hold a sequence of numbers in mind while attending to a simple visual discrimination task of geometric figures. While patients were comparable to controls on performance on each task separately, their performance declined greater than controls when asked to complete these tasks simultaneously. Using Diffusion Tensor Magnetic Resonance Imaging, this difficulty in divided attention was related to a reduction of white matter integrity in the middle frontal gyrus and anterior corona radiata.

Working memory is a related facet of executive function, and allows people to store, process, and manipulate information on a short-term basis. Working memory is different from short term memory in that it allows you to store and 'work with' information, rather than simply retain it. Reports are conflicting as to whether ALS is associated with deficits in working memory. A common task used to assess working memory is the backward digit span test in which participants are read a series of numbers of increasing length and instructed to recall them in reverse order. While some authors report deficient performance of the backward digit span task in ALS (Hanagasi et al., 2002; Lillo et al., 2012a), others have not

(Palmieri et al., 2013; Volpato et al., 2010). In a small but detailed examination of working memory abilities, Hammer, Vielhaber, Rodriguez-Fornells, Mohammadi, and Munte (2011) asked ALS patients to complete an N-Back test, in which they were presented with a sequence of shapes. Participants were asked to identify whether the current shape was in a) the same position (spatial working memory), or b) was the same shape (figural working memory) as that which appeared two images before (i.e., 2-back). Performance on standard neuropsychological measures of working memory showed no impairment compared to controls (i.e., digit span task). However, 35% of patients were unable to complete the N-back task due to an inability to understand the instructions. Of those patients who could complete the task, a demonstrable difficulty was observed in identifying the spatial position of items which previously appeared, whereas figural task performance did not differ from controls suggesting a specific deficit in spatial working memory.

Executive functions also allow people to understand rules and concepts and to be flexible. Concept formation is the ability to mentally categorise, or classify, objects or events and is widely studied using the Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay & Curtiss, 1981). In this test, participants are asked to classify features such as shape, colour, and number of items on each card. No instructions are given as to how cards should be categorised beyond being told ‘correct’ or ‘incorrect’ and the feature to be categorised changes periodically. Through trial and error, participants learn the categorisation system and adapt intermittently to changing rules, requiring both concept formation and cognitive flexibility. While not all studies have demonstrated impairment on the Wisconsin Card Sorting Test (e.g., Palmieri et al., 2009), a recent meta-analysis

of performance in ALS demonstrated that patients complete fewer categorisation trials, made more errors (including perseverative errors), and took longer to learn new rules compared to control participants (Lange et al., 2016). The same authors, through their own experimental study, report that deficits in cognitive flexibility (i.e., shifting between categorisation rules) underlies the observed findings. When simply asked to describe how many ways cards can be sorted (using a similar card sorting test from the Delis-Kaplan Executive Function System), or to recognise categories when presented to them, those with ALS showed reduced performance on concept formation.

Cognitive flexibility can also be understood in terms of task switching (i.e., the ability to shift attention). In addition to the card sorting tests, the Trail-Making Test is often used to assess task switching. However, given the reduction in motor speed present in ALS and its potential to interfere with interpretation, alterations to the scoring mechanism are frequently used. Commonly, a difference score (parts A-B) or a proportion (B/A) have been used with varying results. For instance, Carluer et al. (2015), Hartikainen et al. (1993), and Zalonis et al. (2012) found impaired ALS performance, relative to controls, in Trail-Making difference scores (B-A). Yet Machts et al. (2014) and Palmieri et al. (2009; 2010; 2013) found no impairment for the Trail-Making proportion score (B/A) or difference score (B-A). The independence of these scoring systems from motor speed has yet to be established, perhaps explaining the lack of agreement. Sánchez-Cubillo et al. (2009) found that part A, part B, B-A, and B/A all similarly correlated with a measure of motor speed (finger tapping) in healthy older adults. Indeed, Stukovnik et al. (2010) examined multiple scoring systems for the Trail-Making Test in ALS, reporting that the proportion (B/A) was not significantly impaired in

ALS whereas the difference score (B-A) was significant. After adjustment for motor speed (i.e., time need to produce correct sequence minus time taken to reproduce sequence), these authors note that part B, but not part A, of the Trail-Making Test significantly differs from controls potentially suggesting a deficit in task switching but not processing speed. However, current methods of scoring the Trail-Making Test in the presence of motor impairment requires validation.

As has been noted, executive functions are difficult to examine due to the overlapping functions and often non-specific tests. Kasper et al. (2015) attempted to rectify this limitation and explore which facets of executive dysfunction are most affected in ALS. By re-organising common neuropsychological tests into different aspects of executive function, these authors note that shifting and initiation were most often affected, while updating, inhibition, and problem solving were relatively intact. These findings perhaps make sense given the observations by some authors (e.g., Lange et al., 2016; Stukovnik et al., 2010) that task-switching impairments may underlie some of the profile of executive dysfunction seen in ALS. Furthermore, the preponderance for ALS patients to experience verbal fluency deficits (e.g., Abrahams et al., 1997; 2004) may relate to Kasper et al.'s (2015) cognitive initiation observation.

1.6.2. Verbal fluency

Verbal fluency deficits are one of the most widely recognised markers of cognitive impairment in ALS (Abrahams et al., 1997; Abrahams et al., 2004; Abrahams et al., 2000; Kew et al., 1993), over and above other measures of executive functioning (Stukovnik et al., 2010). For example, Phukan et al. (2012) found that verbal fluency is impaired in 93.8% of patients with executive impairment. Verbal

fluency refers to a person's ability to randomly generate a list of words beginning with a specified letter (letter/phonemic fluency), or a list of semantically related words (category fluency; e.g., names of animals). Successful performance on tests of verbal fluency requires cooperative involvement of language and executive abilities. Individuals must access their lexical store of words, under specified constraints, and continuously monitor their performance to avoid rule breaks and repetition (Shao, Janse, Visser, & Meyer, 2014).

In 2000, Abrahams et al. conducted an extensive investigation of the verbal fluency abilities in ALS aimed at exploring the processes underlying verbal fluency deficits in ALS. Abrahams et al. examined whether intrinsic response generation, phonological loop functions (short term verbal memory), or simple word retrieval were responsible. People with ALS demonstrated general difficulty in letter, semantic, and design fluency tests (the ability to draw random abstract drawings) indicative of a deficit in non-specific intrinsic response generation. Auditory memory for words and sounds, in addition to simple word retrieval were relatively intact in patients. Abrahams et al. (2000) developed the verbal fluency index (VFI) as a measure of verbal fluency, independent of motor impairment. Participants are instructed to say or write as may words as they can that begin with a specified letter (generation condition). The participant is then instructed to re-read, or copy out the previously generated words (control condition). The VFI is calculated using the following equation:

$$VFI = \frac{Time\ given\ for\ generation\ condition - time\ for\ control\ condition}{total\ number\ of\ words\ generated}$$

Letter fluency may be a more specific marker of executive dysfunction and frontal lobe degeneration (Abrahams et al., 1995; Baldo, Schwartz, Wilkins, & Dronkers, 2006; Donaghy et al., 2009; Libon et al., 2009). Imaging studies of verbal fluency in ALS have observed involvement of extensive prefrontal regions, particularly the dorsolateral prefrontal cortex and anterior cingulate cortex using positron emission tomography (PET; Abrahams et al., 1995) and functional magnetic resonance imaging (fMRI; Abrahams et al., 2003; 2004; Sarro et al., 2011; Quinn et al., 2012). Structural imaging studies have also demonstrated prefrontal involvement in fluency performance, such as fronto-temporal white matter association fibres. Pettit et al. (2013) demonstrated correlations between letter fluency performance and white matter integrity of the superior frontal gyrus, inferior frontal gyrus, corticospinal tract, and corpus callosum. In a meta-analysis of verbal fluency performance in patients with focal cortical lesions, Henry and Crawford (2004) demonstrated that letter and semantic fluency were sensitive to both frontal and temporal damage. However, semantic fluency was most strongly associated with temporal damage while letter fluency was most strongly linked to frontal damage (particularly left lateralised).

In combining the evidence of initiation deficits (Abrahams et al., 2000; Kasper et al., 2015), imaging correlates of fluency (Abrahams et al., 1995; Abrahams et al., 2003; Abrahams et al., 2004; Pettit et al., 2013), and the profile of verbal fluency in ALS subgroups (Lepow et al., 2010), impairment in verbal fluency performance may be reflective of prefrontal cortex degeneration.

1.6.3. Social cognition

Social cognition is an umbrella term that describes the cognitive processes necessary for successful negotiation of social situations and interactions. Some authors have suggested that social cognitive deficits may “play a prominent role in clinical care of neurodegenerative conditions” (Elamin, Pender, Hardiman & Abrahams, 2012, *pp*. 1077). For instance, patients become increasingly depending on caregivers as the disease progresses and a breakdown in effective social interaction is likely to have a large impact (Abrahams, 2011). Similarly, a breakdown in the social interaction between clinicians and patients may impact the care provided.

Social cognition encompasses both lower-order processes, such as a person’s response to, and recognition of basic emotions and emotionally-salient stimuli, and higher order processes, such as the ability to interpret the thoughts and actions of others. The recognition of social cognition deficits in ALS has only come about in recent years, despite being recognised as a key feature of FTD. In 2016, Beeldman and colleagues updated their 2008 meta-analysis of cognition in ALS. In the eight-year interval between these two reviews, the most significant change was the addition of social cognition deficits as an integral component of the cognitive profile of ALS. In ALS, social cognition has been studied under two broad components, namely, emotional processing and recognition, and theory of mind (ToM).

Emotional processing and recognition are cognitive processes that describe a person’s response to emotional stimuli (e.g., a picture of a funeral) and the recognition of basic emotions in others (e.g., recognising a person’s expression of fear). People with ALS demonstrate an altered response to

emotionally charged stimuli, in that they rate emotionally charged pictures as being more positive and exciting than controls (Lulé et al., 2005). Furthermore, patients have been shown to rate the faces of strangers with a negative valence as being more approachable (Schmolck, Mosnik & Schulz, 2007) and show a reduced capacity to recognise emotional expressions (Burke et al., 2016a; Girardi et al., 2011; Savage et al., 2014; Zimmerman, Eslinger, Simmons, & Barrett, 2007), particularly negative emotions (Crespi et al., 2014). The suggestion of a selective difficulty in processing negative emotions has be supported by fMRI research (Palmieri et al., 2010), and studies of patients with FTD (Snowden et al., 2008). However, this inability to recognise the emotions of others has not always been consistently found (Papps, Abrahams, Wicks, Leigh, & Goldstein, 2005; Watermeyer et al., 2015), and may be more likely in ALS-FTD (Savage et al., 2014). In a recent meta-analysis, Bora (2017) found that recognition of disgust, surprise, and sadness was reduced in ALS but not anger, fear, or happiness.

In addition to difficulty in the processing and recognition of emotions, patients with ALS have been shown to struggle with ToM in inferring and understanding the thoughts and actions of others. ToM can describe the ability to infer a person's emotional state (*Affective* ToM) (Carluer et al., 2015). On the other hand, *Cognitive* ToM is the understanding that other people may have thoughts or beliefs that are different than one's own (first-order ToM), or that one person might have thoughts and beliefs about a second person's thoughts and beliefs (second-order ToM) (Elamin, Pender, Hardiman, & Abrahams, 2012). A common way of assessing ToM abilities in ALS has been the faux pas test. Here, individuals are read a short story or shown a comic strip in which one of the

characters says something they should not have, and asked to identify the 'faux pas'. Successful completion of the task requires the participant to understand the thoughts and beliefs of story's actor, for example:

"Sally is a three-year-old girl with a round face and short blonde hair. She was at her Aunt Carol's house. The doorbell rang and her Aunt Carol answered it. It was Mary, a neighbour. 'Hi,' Aunt Carol said, 'Nice of you to stop by.' Mary said, 'Hello,' then looked at Sally and said, 'Oh, I don't think I've met this little boy. What's your name?" (Stone, Baron-Cohen & Knight, 1998)

Despite demonstrating intact story comprehension, one third of ALS patients were less able to detect the faux pas compared to controls (Meier, Charleston, & Tippett, 2010). Similarly, Cavallo et al. (2011) presented patients comic strips of social (e.g., a person preparing a romantic dinner) and non-social (e.g., a person changing a lightbulb) situations and asked them to interpret the intentions of the characters. Those with ALS performed worse than healthy controls in interpreting the social cartoons, but not the non-social cartoons indicating a specific difficulty in social understanding.

Assessment of ToM has been extended to demonstrate a reduced ability to interpret eye gaze in ALS. For example, Girardi et al. (2011) and Van der Hulst et al. (2015) attempted to delineate affective and cognitive ToM using the Judgement of Preference Task. Participants were presented with a cartoon face called 'Dina', which looked at one of four items. Those with ALS were asked 'which picture does Dina love?' (affective ToM), or 'which picture is Dina thinking of?' (cognitive ToM). Van der Hulst et al. found that 36% of patients displayed an affective ToM impairment and 27% displayed a cognitive ToM impairment. Performance on cognitive ToM tasks has been linked to degeneration of medial

prefrontal, dorsolateral prefrontal, and supplementary motor cortices in ALS (Carluer et al., 2015). Conversely, affective ToM abilities have been associated with the anterior cingulate cortex and the right inferior frontal gyrus (Cerami et al., 2014).

Debate continues as to the source of social cognitive impairments in ALS. Cavallo et al. (2011) and Meier et al. (2010) found social cognitive deficits to be independent of executive function. Yet, many studies which have explored social cognition in ALS have suffered from small sample sizes, reducing their power and interpretability. Larger studies have suggested strong connections between the two (Burke et al., 2016b; Gibbons et al., 2007; Snowden et al., 2003; Watermeyer et al., 2015). Others suggest that social cognition relies on the brain's ability to 'simulate' the actions of others, thereby allowing for internal comprehension and inference (Gallese, Keysers, & Rizzolatti, 2004; Jelsone-Swain, Persad, Burkard, & Welsh, 2015), however this hypothesis requires further investigation. The meta-analysis by Bora (2016) suggested that while executive dysfunction explains some of the variance in social cognitive abilities, a significant proportion of the variance remains unexplained.

1.6.4. Language

Psycholinguistics covers a broad range of cognitive skills necessary for the use, comprehension, and production of language. Language is recently recognised as an important cognitive domain affected in some ALS cases. Impaired performance has been observed in higher-order language, such as grammar (Ash et al., 2015; Tsermentseli et al., 2015). However, basic language functions, such as naming, have also been the subject of language research in ALS. Tests,

such as the Graded Naming Test or the Boston Naming Test, present participants with pictures of objects which are to be named. Some research has suggested that naming deficits are present in ALS (e.g., Cavallo et al., 2011; Hanagasi et al., 2002). Abrahams et al., (2004) demonstrated that ALS patients had reduced activation in regions involved in confrontation naming (Abrahams et al., 2003), including bilateral inferior frontal gyri (including Broca's area) and right cingulate gyrus. As such, naming appears to be affected in patients with ALS. However, not all authors have consistently demonstrated a naming deficit in ALS (Gibbons et al, 2007; Pettit et al., 2015). This inconsistency may be due to the findings that people with ALS may have a particular difficulty in processing verbs or action-words compared to nouns (Bak & Chandran, 2012). Many naming tests, including the Graded and Boston Naming Tests, rely on the processing of objects or nouns, whereas studies that have assessed the verb/action-word abilities of patients have more consistently found deficits (Grossman et al., 2008; Taylor et al., 2013).

Some authors have suggested that this selective action-verb impairment may be due to a greater executive involvement in verb processing (e.g., Bak & Hodges, 2004), however, more recently this verb-noun dissociation has been attributed to the role of the motor cortex in language processing. Imaging studies have suggested that in addition to the prefrontal cortex, the motor cortex may play a role in action word processing (e.g., York et al., 2014). For example, in one study, participants were asked to move their tongue, feet, and fingers while undertaking fMRI. Participants were then asked to passively read words associated with these body parts (e.g., chew, lick, kick). Areas of the motor cortex that activated during the movement condition matched (either directly overlapping, or directly adjacent) to areas of the brain that activated during the

reading condition (Hauk, Johnsrude, & Pulvermüller, 2004). These findings suggest that the motor cortex is important for processing action words and that these correspond to areas of the brain responsible for the actual movement. However, other authors have argued strongly that this is not the case (For instance, see de Zubicaray, Arciuli, & McMahon, 2013). Watson, Cardillo, Ianni, and Chatterjee (2013) conducted a meta-analysis of patterns of cerebral activation associated with action words and images. The authors report that visual motor areas were consistently recruited but not motor or pre-motor areas. Rather, action words and images activated distinct but overlapping areas of the visual motor cortex (i.e., middle temporal visual area). Whereas action images related to the occipital cortex and visual motor area bilaterally, action words related to left middle and inferior temporal gyri and hippocampus.

In addition to retrieving the correct word, an important aspect of language function concerns word meaning. Semantic memory is the aspect of language functions that describes a person's understanding of word meaning. The Pyramid and Palm Trees Test was developed to assess semantic memory functions (Howard & Patterson, 1992). Here, participants are presenting with either a single word or a picture above two other words or pictures and asked to select which of the bottom items is most like the top item. However, the Pyramid and Palm Trees Test is noun/object based, and may not necessarily best reflect the previously noted profile of language deficits observed in ALS. To address this limitation, Bak and Hodges (2003) developed the Kissing and Dancing Test, which includes items from the Pyramid and Palm Trees Test, but also includes stimuli measuring action/verb knowledge. For example, participants are asked to select which of two options semantically relates to that of a person writing a letter. The individual

is given the option of a person typing or a person stirring a hot drink. The Kissing and Dancing Test has been shown to be impaired in ALS (Taylor et al., 2013, van der Hulst et al., 2015) to a greater degree than the Pyramid and Palm Trees Test (Bak & Hodges, 2003).

It has been suggested that language impairment in ALS may be reflective of subclinical presentations of language-variants FTD (Abrahams, 2013a). Leslie et al., (2015) examined the semantic abilities of ALS, ALS-FTD, and semantic dementia patients. A gradation of impairment was observed (i.e., controls > ALS > ALS-FTD > SD) where 33.3% of ALS patients, 73.3% of ALS-FTD, and 100% of semantic dementia patients demonstrated deficits in semantic knowledge which was associated with degeneration of the temporal poles. However, pure semantic dementia is rarely seen in ALS suggesting a different relationship than that with behavioural variant FTD. A recent study by Taylor et al. (2013) showed that when tested using a battery of language and executive neuropsychological tests, 43% of ALS patients presented with language dysfunction and 31% with executive dysfunction. While 44% of the variance in language function was explained by executive functioning, suggesting a significant degree of overlap, the largest proportion of variance remained unexplained.

1.6.5. Memory

Memory functions are one of the most widely studies areas within psychology and one of the most common reported symptoms of brain injury and disease (Evans, 2013). Memory function describes our ability to encode, store, and retrieve information. In ALS, research has been focused on the *type* of information being processed (i.e., verbal and visual information); the capacity for

consolidation (i.e., immediate memory compared to delayed memory); and whether the retrieval of information is by direct recall (e.g., being asked to recall a list of previously learned words) or recognition (e.g., being given a list of words and asked to identify which you were asked to learn).

Impairments in memory have been found by some researchers (Christidi et al., 2012; Raaphorst et al., 2015), while others have found memory to be largely intact (Cuddy, Papps, Thambisetty, Leigh, & Goldstein, 2012). Most commonly however, researchers report mixed results, for example, intact immediate recall but impaired delayed recall (Mantovan et al., 2003), intact immediate recognition but impaired delayed recognition (Machts et al., 2014; Munte et al., 1998), or intact recall but impaired recognition (Machts et al., 2014). Some studies even found patients to be both impaired and intact depending on the type of test used, for example, list learning compared to story recall (Christidi et al., 2012).

It has been suggested that problems with memory may be associated with emotional functioning. While healthy adults' memory for information can be enhanced when information has an emotional component (e.g., "burn" compared to "bowl"), those with ALS did not show a similar benefit (Cuddy et al., 2012; Papps et al., 2005). Furthermore, observed deficits in memory may be partly explained by dysfunction of other cognitive domains, such as executive functioning (Christidi et al., 2012; Mantovan et al., 2003). However, Machts et al. (2014) found that executive functioning only explains 20.5% of the variability in memory performance in ALS, leaving a significant proportion of the variance unexplained. Additionally, dysfunction in learning and resistance to interference,

which are related to executive functioning, may be the most prominent memory difficulties of patients with ALS and ALS-FTD (Kasper et al., 2015).

A few neuroimaging studies have suggested that brain regions responsible for various facets of memory, particularly the hippocampus, may be affected in ALS (Takeda, Uchihara, Arai, Mizutani, & Iwata, 2009; Takeda, Uchihara, Mochizuki, Mizutani, & Iwata, 2007). It is suggested that pathological TDP-43 deposition occurs in the hippocampus in late stage disease (Brettschneider et al., 2013). Given that late-stage disease patients are often excluded from cognitive research (i.e., a forced vital capacity of less than 70% predicted), it may be that memory involvement is under-recognised in ALS, and that memory involvement is dependent on disease stage.

1.6.6. Visuospatial functions

Visuospatial functions describe skills necessary to identify, locate, and manipulate objects in a person's visual environment. These abilities allow us to perform routine activities, such as driving, walking, recognising loved ones, and interpreting the motor actions of others. In the realms of FTD, visuospatial changes appear to be mediated by higher-order executive dysfunction, rather than due to simple perceptual difficulties (Possin, 2010; Possin et al., 2012). Thompson, Stopford, Snowden, and Neary (2005) compared the visuospatial abilities of patients with FTD and Alzheimer's disease by asking patients to copy complex line drawings. While patients with Alzheimer's disease made errors in the spatial location of the drawing's various elements, FTD patients made errors in organisation and perseveration.

Studies that have examined the visuospatial abilities in ALS have generally found that patients perform within normal ranges (Lillo & Hodges, 2009), although some studies have found impairments (Hanagasi et al., 2002; Machts et al., 2014). However, the tasks used generally rely on processing line-drawings, rotating blocks, or spatial location judgements. Fiori et al. (2013) found that while people with ALS could visualise and manipulate inanimate mental imagery (letters), they were less able to visualise and manipulate mental imagery concerning body parts (e.g., rotating hands). It is hypothesised that the ability to understand motor actions may rely on the ability to 'simulate' this in the motor cortex of the brain (Hesslow, 2002). Connections have been suggested between the motor cortex and other cognitive functions, such as social cognition (Jelsone-Swain et al., 2015), action words and verb processing (Bak & Chandran, 2012; Hauk, Johnsrude, & Pulvermüller, 2004), and verbal fluency (Abrahams et al., 1995; Grogan et al., 2009). However, as previously noted, this relationship is debated (e.g., Watson et al., 2013). It is likely that deficits in visuospatial ability in ALS may be accounted for by executive failures, rather than true visuospatial failures but this area remains under-studied.

1.7. Behaviour in ALS

Behaviour in ALS has received significantly less attention than cognition. Yet, as with FTD, behavioural features are common in ALS and are marked by changes in personality, social conduct, manners, and decorum. Behaviour change in ALS is often mild except in cases of ALS-FTD, and variable. For instance, Raaphorst, Beeldman, De Visser, De Haan, and Schmand (2012a) conducted a systematic review of studies examining behaviour change in ALS noting 59 different

symptoms were reported in included research. The subjective and contextual nature in what constitutes a 'behaviour' has limited the objectivity of measurement, and as such, research tends to focus on behaviour as a unitary symptom. Yet, Behaviours can appear as a single symptom, or constellation of symptoms. Common themes have emerged from the FTD literature operationalised in recent diagnostic criteria. Diagnostic criteria for behavioural variant FTD is based on the presence of behavioural features including disinhibition; apathy; loss of sympathy or empathy; perseverative, compulsive, or stereotypical behaviours; and altered eating behaviours (Rascovsky et al., 2011).

Disinhibition describes a reduction in an individual's ability to inhibit thoughts or desires that may be socially inappropriate. For example, making rude, offensive, or sexual comments or jokes; violating social norms, such as inappropriate physical contact with strangers; or making decisions that are careless or impulsive, such as new-onset gambling, stealing, or selling property without regard for the consequences. Caregivers have reported increases in disinhibited behaviour following the onset of ALS (Girardi et al., 2011; Grossman, Woolley-Levine, Bradley, & Miller, 2007; Terada et al., 2011; Van der Hulst et al., 2015). However, Grossman et al. (2007) also noted that caregivers report features of behaviour dysfunction prior to disease onset, perhaps suggesting that behavioural features may precede motor dysfunction. Despite the noted increases in disinhibited behaviours from pre- to post-illness, studies tend to suggest that rates of disinhibition are lower than other behaviours. For example, Girardi et al. (2011) and van der Hulst et al. (2015) found that disinhibition significantly increased from pre- to post-illness, but that post-illness levels of disinhibition did not differ from controls. Other authors have similarly suggested

that rates of disinhibition are relatively low (Lillo et al 2011; Raaphorst et al 2012a) with Abrahams et al. (2014) reporting it to be the least reported behaviour change. Hsieh et al., (2016) report that behavioural disinhibition may be uncommon until later in the disease course perhaps explaining the observed infrequency.

Apathy, demotivation, or inertia is the most commonly reported behavioural feature of both ALS and FTD (Chiò et al., 2010; Grossman et al., 2007; Kasper et al., 2015; Lillo et al., 2011; Meier et al., 2010; Watermeyer et al., 2015; Witgert et al., 2010). A person may appear to lose drive, interest, or motivation to do things. Similarly, a person may require prompting to initiate or maintain common daily tasks such as self-care or cleaning. It is suggested that apathy is multidimensional in nature (Levy & Dubois, 2006). In reviewing and collating the available models of apathy subtypes, Radakovic and Abrahams (2018) proposed the Dimensional Apathy Framework consisting of initiation, emotional, and executive apathy. Initiation apathy describes a lack of motivation for the instigation of self-directed thinking or behaviour, executive apathy is a lack of motivation for attention, organisation, and planning, in that patients are demotivated to commit to goal directed behaviour, while emotional apathy is akin to emotional neutrality or indifference to oneself and one's surroundings. In ALS, levels of executive apathy are similar to control samples, however, initiation apathy is a prominent feature (Radakovic et al., 2016). Conversely, executive apathy appears to profile apathy symptoms in Parkinson's disease (Radakovic, Davenport, Starr, & Abrahams, 2017a), while Alzheimer's disease possesses a heterogeneous apathy profile (Radakovic, Starr & Abrahams, 2017b). The presence of initiation apathy may share a common underlying mechanism to observed deficits in verbal fluency (Abrahams et al., 2004; Grossman et al., 2008;

Radakovic et al., 2017c). The profile of multidimensional apathy in ALS has recently been validated in a large Italian cohort of ALS patients. Like Radakovic et al. (2016), Santangelo et al. (2017) found initiation apathy to be the most prominent form of apathy in ALS.

Another behavioural symptom in ALS is a loss of sympathy and empathy. This behaviour can manifest in a diminished response to the needs and feelings of others, or demised interest in socialising and being close to others. For example, making hurtful or thoughtless comments without regard for other people's feeling, or a lack of interest in being socially or emotionally close to others. Loss of sympathy/empathy has been relatively understudied due to its absence from common measures of behaviour (e.g., Frontal Systems Behaviour Scale, Neuropsychiatric Inventory, Cambridge Behaviour Inventory). However, Abrahams et al. (2014) found that rates of loss of sympathy/empathy was the second most common behavioural feature after apathy.

People with ALS may also demonstrate perseverative, stereotyped, or compulsive behaviours. These behaviours can be analogous to obsessive-compulsive behaviours and marked by simple repetitive movements (e.g., clapping, tapping, or rocking), more complex behaviours (e.g., such as hoarding, counting, cleaning rituals), or stereotyped speech (e.g., repeating single words or phrases). Unfortunately, research on perseverative behaviours in ALS are lacking.

Changes in diet or eating behaviours can be perhaps the most objective behaviour to observe. Patients may develop cravings for particular types of food, especially sweet foods or carbohydrates, or continue to eat despite satiety. Patients may also explore inedible objects with the mouth, or smoke

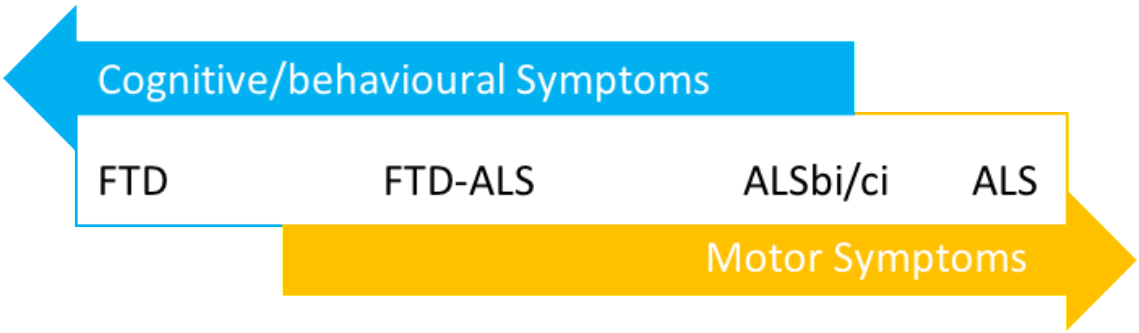
compulsively. In the only systematic study of eating behaviours across the ALS-FTD spectrum, Ahmed et al. (2016a) demonstrated a range of behavioural changes. These changes were associated with disease duration and neuropsychological status, such that pure ALS patients experienced fewer eating behaviours, followed by ALS patients with cognitive or behavioural impairment, and finally patients with ALS-FTD/FTD. Ahmed et al. demonstrated changes in appetite, eating habits (i.e., stereotyped eating behaviours), food preferences and intake (e.g., sweet, carbohydrate, fat), and oral behaviours (e.g., cramming, smoking). It has been suggested that changes in eating behaviours may be protective of survival (Ahmed et al., 2016a; 2016b)

A final behaviour common but non-specific to ALS and absent from the FTD diagnostic criteria is that of emotional lability. Described as pathological laughing, crying, and the recent addition of pathological smiling (Newsom-Davis, Abrahams, Goldstein, & Leigh, 1999), emotional lability can be highly variable and is estimated to affect 10-71% of patients (Gibbons, Richardson, Neary, & Snowden, 2008; Newsom-Davis, et al., 1999; Palmieri et al., 2009). Patients may laugh, cry, or grimace at an inappropriate time or place or when you would not expect it, for example laughing when angry. Emotional lability has been linked to the prefrontal cortex and executive functioning in ALS (Hübers et al., 2016; McCullagh, Moore, Gawel, & Feinstein, 1999). It can be present at early stages of the disease and is thought to be more common in patients with bulbar symptoms (Palmieri et al., 2009; Tortelli et al., 2016).

1.8. The profile of cognitive and behaviour change in ALS

Cognitive impairment has been established as common non-motor features of ALS. Studies reporting the prevalence of impairment in ALS have suggested that cognitive deficits (see Table 1.2) are present in approximately 35% of patients (Grossman et al., 2008; Massman et al., 1996; Murphy et al., 2016; Phukan et al., 2012; Ringholz et al., 2005). Some authors have suggested classification systems, such as Phukan et al. (2012), in which patients are classified as being cognitively intact, having executive impairment (ALS-Ex), non-executive cognitive impairment (ALS-NECI), or ALS-FTD. In such cases, 21% were classified as ALS-Ex, 14% as ALS-NECI, and 14% ALS-FTD. Using the same categorisation system, Montuschi et al., 2015 categorised 20% as ALS-Ex, 5.5% as ALS-NECI, and 13% as ALS-FTD. Commonly however, Strong and Colleagues' (2009) consensus criteria are used to direct classification of neuropsychological status in ALS (as described in Figure 1.4).

Figure 1.4. ALS-FTD spectrum



These criteria recommend the classification of patients based on their cognitive and behavioural profile. ALSci (cognitive impairment) and ALSbi (behavioural impairment) describe patients who present with predominantly

cognitive or behavioural symptoms, but do not meet criteria for ALS-FTD. Patients classified at ALSci must demonstrate cognitive impairment in at least two distinct tests sensitive to executive functioning, whereas, patients classified as ALSbi must present with two non-overlapping behavioural features. To meet criteria for ALS-FTD, patients must possess signs of FTD as described in the Neary criteria (Neary et al., 1998). Rascovsky et al. (2007) notes that the Neary criteria contain significant limitations and proposed a revised diagnostic criteria for FTD (Rascovsky et al., 2011). The Rascovksy criteria specifies the need for a progressive deterioration of cognition and/or behaviour, marked by the presence of three symptoms from Table 1.3. Unfortunately, the Strong classification system, and the Rascovksy criteria is limited owing to the presence of cognitive deficits other than executive functioning in ALS. Additionally, substantial overlaps exist between ALSci and ALSbi, in a form of ALScbi (Murphy et al., 2016; Murphy et al., 2007).

The Strong consensus criteria was updated in 2017 (Strong et al., 2017), modifying the criteria for ALSci, ALSbi, and ALS-FTD. ALSci is characterised by evidence of executive dysfunction (including social cognition), language dysfunction, or a combination of the two. Executive dysfunction is now defined as the presence of letter fluency impairment or impairment on two non-overlapping measure of executive functions. Language impairment is defined as impairment on two non-overlapping tests of language function. On the other hand, ALSbi is defined by the presence of apathy with or without other behavioural changes, or the presence of two or more behavioural features a) disinhibition, b) loss of sympathy and empathy, c) perseverative, stereotyped or compulsive behaviour, d) hyper- orality/dietary change, e) loss of insight, f) psychotic symptoms (e.g.

somatic delusions, hallucinations, irrational beliefs). While the updated guidelines (see Table 1.4) have incorporated the expanded understanding of the neuropsychological profile of ALS, these changes have not yet been validated or externally examined.

Table 1.4. Revised Strong Consensus Guidelines for the characterisation of neuropsychological symptoms in ALS

Heading	**Axis II. Neuropsychological characterisation**
ALSbi	A diagnosis of ALSbi requires: 1) The identification of apathy with or without other behaviour change; OR 2) meeting at least two non-overlapping supportive diagnostic features from the Rascovsky criteria (Rascovsky et al., 2011).
ALSci	A diagnosis of ALSci depends on evidence of either executive dysfunction (including social cognition) or language dysfunction or a combination of the two. Executive impairment is defined as: 1) Impaired verbal fluency (letter); OR 2) Impairment on two other non-overlapping measures of executive functions (which may include social cognition). Language impairment is defined as: 1) Impairment on two non-overlapping tests and in which language impairment is not solely explained by verbal fluency deficits.
ALScbi	Patients who meet the criteria for both ALSci and ALSbi
ALS-FTD	A diagnosis of ALS-FTD requires: 1) Evidence of progressive deterioration of behaviour and/or cognition by observation or history; AND 2) The presence of at least 3 of the behavioural/cognitive symptoms outlined by Rascovsky et al. (2011); OR 3) The presence of at least 2 of those behavioural/cognitive symptoms, together with loss of insight and/or psychotic symptoms; OR 4) The presence of language

Table 1.3. Rascovsky Criteria for the diagnosis of FTD

	Possible FTD
1	Early behavioural disinhibition marked by one of the following: a. Socially inappropriate behaviour b. Loss of manners or decorum c. Impulsive, rash or careless actions
2	Early apathy or inertia marked by <u>one</u> of the following: a. Apathy b. Inertia
3	Early loss of sympathy or empathy marked by one of the following: a. Diminished response to other people's needs and feelings b. Diminished social interest, interrelatedness or personal warmth
4	Early perseverative, stereotyped or compulsive /ritualistic behaviour marked by <u>one</u> of the following: a. Simple repetitive movements b. Complex, compulsive, or ritualistic behaviours c. Stereotypy of speech
5	Hyperorality and dietary changes marked by <u>one</u> of the following: a. Altered food preferences b. Binge eating, increased consumption of alcohol or cigarettes c. Oral exploration or consumption of inedible objects
6	Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions marked by the presence of <u>all</u> of the following: a. Deficits in executive tasks b. Relative sparing of episodic memory c. Relative sparing of visuospatial skills
	Probable FTD
	Meets criteria for possible FTD in addition to: a. Significant functional decline b. Imaging results demonstrating frontal and/or anterior temporal lobe atrophy, hypoperfusion, or hypometabolism
	Definite FTD
	Meets criteria for possible or probably FTD in addition to: a. Histopathological evidence of FTD on biopsy or at post-mortem b. Presence of known pathogenic mutation

Note. The above table is adapted from Strong et al., (2017)

1.9. Cognition and behaviour summary

Most frequently, executive functions, fluency, and more recently, language and social cognitive functions appear to be affected in ALS, and may in part be

explained by degeneration of the prefrontal and temporal lobes. A summary of the main findings of cognitive research in ALS is displayed in Appendix I. Regarding behaviour, apathy is the most commonly reported behavioural feature, with loss of sympathy/empathy, perseverative, and eating behaviours also reported. The independence of cognitive and behavioural symptoms remains to be established, but previous research would suggest that there exists a considerable overlap. Higher-order executive functioning appears to moderate some of the findings in language, social cognition, and fluency deficits. For example, Taylor et al. (2013) found that executive functioning explained 44% of the variance in language functioning and Phukan et al. (2012) found that 94% of patients with executive dysfunction also demonstrated verbal fluency deficits. Similarly, Watermeyer et al. (2015) revealed that executive functioning significantly correlated with social cognition (r = .61), which, after controlling for relevant variables, significantly predicted social cognitive performance (standardized Beta = .49). Despite the potential overlap, a considerable amount of variance remains unexplained, suggesting that these domains work independently but also in conjunction. Deficits in memory and visuospatial functions have also been demonstrated, but these results are less consistent.

Beeldman and colleagues' (2016) meta-analysis suggests that all cognitive domains, bar visuospatial functioning, demonstrate significant effect sizes. Fluency, language, and social cognition possess the largest effect sizes, with visual and verbal memory, attention, and executive functioning demonstrating smaller effect sizes. With the frequency of cognitive symptoms in ALS, it is important to note that substantial heterogeneity continues to exist. Executive functions, delayed verbal memory, and psychomotor speed possessed

the greatest heterogeneity, with language and social cognition possessing moderate heterogeneity. Fluency, immediate verbal memory, visual memory, and attention showed the least heterogeneity compared to other domains of cognition (Beeldman et al., 2016). Some of the heterogeneity may be explained in the continuing use of cognitive tasks that do not account for motor impairment. Alternatively, the variance may be explained by a relationship between disease severity and cognition (e.g., Elamin et al. 2013), or by undetected sub-clinical phenotypes of dementia (e.g., semantic dementia).

Research concerning ALS has sought to explore how cognition and behaviour are affected separately, or in parallel. However, surprisingly little has been done to explicitly to explore how these sets of symptoms relate to one another. Relationships have been suggested between verbal fluency and behavioural symptoms (Gordon et al., 2007; Raaphorst, Beeldman, Schmand, et al., 2012b), in particular apathy (Grossman et al., 2007; Radakovic et al., 2017c), and between emotional lability and errors made on the Wisconsin Card Sorting Test (McCullagh et al., 1999). One study that did explore the relationship between behaviour and cognition in-depth was that of Witgert et al. (2010) who found apathy to significantly relate to verbal fluency, cognitive flexibility, attention, and visuospatial abilities.

Stuss and colleagues have suggested a model for executive functions in which areas of the frontal lobes may be related to discrete, but overlapping, abilities (2007; 2011). The model forms a fractionated rethinking of the supervisory attention system (Norman & Shallice, 1986) and supposes that there exists no single organising function, but rather independent regulatory processes linked to discrete brain regions. Energization describes the initiation and

maintenance of response; monitoring/task-setting is the ability to monitor performance accuracy and adjust to changing circumstances; emotion/behaviour regulation integrates emotional, social, and reward-risk aspects of cognition; while metacognition is the ability to integrate other facets of frontal lobe functions to complete a task (Stuss et al., 2007; 2011). It is posited that energisation relates to dorsomedial prefrontal function; task-setting/monitoring relates to the left and right dorsolateral prefrontal cortex respectively; emotion/behaviour regulation to the lateral and medial orbitofrontal areas; and metacognition relates to the rostral prefrontal cortex.

In their exploration of these component structures in patients with ALS, Gillingham and colleagues (2016) demonstrated specific deficits in energisation, and monitoring/task-setting despite normal performance on a battery of standard clinical tests. This finding may explain and connect some of the observed deficits in ALS. Verbal fluency impairment is commonly reported in ALS suggestive of a deficit in intrinsic response generation (Abrahams et al. 2004), which falls under the energization component of the Stuss model (Stuss et al. 2007). Verbal fluency has been related to apathy in ALS (Grossman et al. 2007; Radakovic et al., 2017c). Additionally, the multicomponent view of apathy in ALS (Radakovic et al., 2015) suggests a prominent involvement of initiation apathy (motivation for the instigation of self-directed thinking or behaviour). Taken together, this evidence suggests that verbal fluency deficits and apathy may share common underlying frontal-lobe pathology. Recently, Radakovic et al. (2017c) evaluated the relationship between cognition and apathy dimensions. ALS patients demonstrated a significant difference in tasks of intrinsic response generation and social cognition compared to controls. Radakovic and colleagues showed

that intrinsic response generation, or energizing, as measured with a task of verbal fluency significantly related to initiation apathy.

Monitoring and task-setting are also affected in ALS (Stuss et al. 2007; 2011), which is important for learning stimuli-response relationships, monitoring performance over time (e.g., detecting errors, timing), which may underlie deficits observed using the Wisconsin Card Sorting Task (Lange et al., 2016). Reported cognitive inhibition difficulties using the Stroop Colour-Word Test (Christidi et al., 2012; Zalonis et al., 2012) and the Hayling Sentence Completion Task (Carluer et al., 2015; Lillo, et al., 2012a) may share common processes with behavioural disinhibition in that they both require inhibiting internal reactions to external stimuli. The relative infrequency of behavioural disinhibition (e.g., Abrahams et al., 2014) compared to other behavioural features may help to understand the inconsistency with which cognitive inhibition deficits are observed (e.g., Girardi et al., 2011; Taylor et al., 2013).

Similarly, at face value, a behavioural loss of empathy may be related to the observed ToM deficits in ALS, emotional processing, and emotional recognition. While the relationship between behavioural symptoms and social cognition has been suggested previously in FTD (Adenzato, Cavallo, & Enrici, 2010), to our knowledge, Radakovic et al. (2017c) is the only study to examine this. These authors report that emotional recognition significantly correlated with emotional apathy. However, evidence suggests that ALS results in reduced capacity to interpret the emotional expressions of others (Crespi et al., 2014; Girardi et al., 2011; Savage et al., 2014; Zimmerman et al., 2007), and that ToM deficits can be specific to interpreting others' emotional state (van der Hulst, Bak & Abrahams, 2015), may partly explain this behavioural manifestation.

1.10. Cognition, behaviour, and disease variables

Some researchers have attempted to link neuropsychological status with physical disease symptoms. While many studies have found little to no relationship between cognitive, behavioural, and physical symptoms (Consonni et al., 2013; Elman & Grossman, 2007; Lillo, Garcin, Hornberger, Bak, & Hodges, 2010; Lillo et al., 2011; Ringholz et al., 2005; Terada et al., 2011; Witgert et al., 2010; Woolley, Zhang, Schuff, Weiner, & Katz, 2011), others have found a relationship. Associations between cognitive functioning and respiratory function in ALS has been suggested (Murphy et al., 2016; Newsom-Davis, Lyall, Leigh, Moxham, & Goldstein, 2001; Piepers et al., 2006) with memory and fluency performance significantly worse in patients in respiratory failure (Kim et al., 2007), but that performance may be partially corrected by non-invasive ventilation (Newsom-Davis et al., 2001). Lomen-Hoerth et al. (2003) found that ALS-FTD patients were more likely to have a lower FVC reading and family history of dementia compared to non-demented group despite having similar ALSFRS-R scores.

1.10.1. Neuropsychological function and bulbar involvement

Site of onset (i.e., bulbar versus limb onset) is often studied with regards to cognitive and behavioural symptoms, with some suggesting that bulbar onset ALS patients are more likely to experience neuropsychological dysfunction (Burke et al., 2016a; Montusichi et al., 2015; Murphy et al., 2016). Yet, results of these studies are inconsistent with many researchers unable to find such a relationship (Cavallo et al., 2011; Lillo et al., 2012a; Lomen-Hoerth et al., 2003; Taylor et al., 2013; Zalonis et al., 2012). This inconsistency may be due to the

way in which bulbar onset is conceptualised. Some researchers have explored whether bulbar involvement, and not onset, relates to neuropsychological functioning. By grouping patients by region of onset, those with limb-onset may have bulbar signs and vice versa distorting groupings. Abrahams et al. (1997) explored such a relationship and observed that executive impairment was more prominent in patients with pseudobulbar involvement (i.e., upper motor neuron). In a large-scale study, Ringholz et al. (2005) using a sample 279 patients reported no relationship between region of onset and cognition, but did report that patients with cognitive impairment are significantly more likely to have dysarthria. Similarly, in a sample of 175 patients, Sterling et al. (2010) reported that dysarthria significantly related to executive functioning, even after controlling for motor speed. With regards to behaviour, Santangelo et al. (2017) reported that apathetic and non-apathetic ALS cases differed on the ALSFRS-R with respect to bulbar functioning.

1.10.2. Neuropsychological function and disease progression

Whether cognition and behaviour change over the course of the disease is of clinical importance in ALS. Cross-sectional studies have used the ALSFRS-R as a proxy of disease progression. Associations have been observed between verbal fluency and functional status (Palmieri et al., 2009), and between symptom duration, functional status, rate of progression, and cognition (Gordon et al., 2010b). More recently, a study by Murphy et al. (2016) including 286 patients demonstrated that behavioural symptoms, in particular apathy, and reduced language output, were significantly associated with functional status, respiratory function, and emotional lability. Unfortunately, the ALSFRS-R has a

heterogeneous trajectory for individuals and is curvilinear. As such, it may not be accurate as a measure of disease progression (see section 1.4.1).

A recent cross-sectional study attempted to estimate disease progression using the King's Clinical Staging System (Roche et al., 2012; see section 1.5.2). Executive and memory functioning significantly differed in line with advancing disease stage (Trojsi et al., 2016). Unfortunately, this study suffered from fundamental design limitations. The study is underpowered once groups were split into disease stages and no control group was included. Additionally, the authors did not control for motor speed in their cognitive evaluations, which is particularly pertinent given the lower ALSFRS-R scores corresponds to later disease stages. The Addenbrooke's Cognitive Examination Revised used in this study, like other non-adapted screening instruments (e.g., the Montreal Cognitive Assessment or the Frontal Assessment Battery), can often not be administered to a significant proportion of people with ALS due to motor weakness and exaggerate performance deficits (Abrahams, 2013b; Burkhardt et al., 2017; Lulé et al., 2015; Xu et al., 2017).

Several studies have attempted to trace the progression of behavioural and cognitive symptoms over time directly using longitudinal designs. Longitudinal studies of cognition are variable, suffering from small sample sizes, presence of practice effects, short test-retest intervals, and large rates of attrition (See Table 1.5 for summary). Kilani et al. (2004) found no difference in cognitive performance over time in their small study. Robinson et al. (2006) found no significant effect over six months when patients were viewed as a group. However, 36.84% of patients developed abnormal scores on tests of memory, executive, and visuospatial functioning. Abrahams, Leigh, and Goldstein (2005a),

Gordon et al. (2010b) and Schreiber et al. (2005) found mixed results where performance on some cognitive tasks got worse (e.g., word finding), some remained stable (e.g., verbal fluency), while others even improved (e.g., visuospatial). Kasper et al. (2016) explored longitudinal changes in executive functioning over time. No significant effect was observed, however, this study included non-ALS phenotypes, and split patients by cognitive status resulting in small group sample sizes. A recent large-scale study by Elamin et al. (2013) found that certain tasks of memory, language, and visuospatial functioning declined over time. Decline in memory functions were related to baseline performance in that patients with baseline memory impairment decline more quickly compared to patients with baseline executive impairment.

The state of the literature regarding the relationship between cognition, behaviour, and physical factors is far from conclusive. As described in Table 1.5, these longitudinal studies suffer from design limitations which restricts their interpretability and generalisability. Previous studies have suffered small sample sizes and not controlled for practice effects, which may obscure any decline in cognition and behavioural functioning. Furthermore, high attrition will likely result in the retention of only the most cognitively, behaviourally, and physically healthy participants and research to date has not accounted for attrition in data analysis. Further research is needed to explore how, and if, cognitive, behavioural, and physical symptoms are related. Only one study to our knowledge has explored longitudinal changes in behaviour, and while it found no significant changes over time, its sample size was small and the majority of patients dropped out before repeat testing could be conducted (De Silva et al., 2016).

Table 1.5. Summary of longitudinal cognitive studies in ALS

Study	Design	Findings	Critique
Kilani et al. (2004)	19 ALS (n_2 = 14, n_3 = 13) and 19 controls (n_2 = 19, n_3 = 19) tested at baseline, 6 months, and 12 months	Significant decline in task switching (TMT B and B-A). No significant change over time observed in concept formation (WCST), memory (Rey Memory Test), visuospatial (BVRT), RPM, language (BNT)	Small sample size. No control for motor speed in neuropsychological tests. Time used as proxy of progression. No control for attrition.
Abrahams et al. (2005a)	20 ALS and 18 controls tested twice over 6 months	No significant deterioration in verbal fluency (spoken or written), language (GNT), visuospatial (JLO). Significantly slower computerised sentence completion task performance over time.	Small sample size, time used as proxy of disease progression. Cognitive tests corrected for motor speed.
Schreiber et al. (2005)	52 ALS, four time points, four-month interval (n_2 = 32, n_3 = 24, n_4 = 19)	Significant decline in perceptual interference (CWIT naming time), memory (AVLT learning achievement). Significant improvement in letter fluency (COWAT ratio words/errors), design fluency (5-PFT number of errors, ratio of number/errors), memory (AVLT loss by interference). No significant change in letter fluency (COWAT words and errors), design fluency (5-PFT number of designs), concept formation (WCST), perceptual interference (CWIT interference time, error score), memory (DS, RFT, AVLT words delayed recall and recognition), attention (TAP)	No control group and no control for practice effects. Longitudinal analysis only conducted on patients who completed all time points. No control for motor speed. No adjustment for multiple comparisons. Time used as proxy of progression.
Robinson et al. (2006)	19 ALS and 8 controls tested twice over 6 months	No significant decline in attention (DS forward), working memory (DS backward), verbal memory (RAVLT), language (PVLT), visuospatial (Object Decision test and Efron Shapes Discrimination test), executive functions (RPM, WCST). However, 36.8% developed abnormal performance over follow-up, most commonly in verbal memory and WCST.	Small sample size. Use of 1 standard deviation for abnormality. Time used as proxy of progression.

Elamin et al. (2013)	186 ALS (n_2 = 98, n_3 = 46, n_3 = 11) and 120 controls (n_2 = 58, n_3 = 31, n_4 = 10) tested at baseline, 6 months, and 12 months	Significant decline in visuospatial functioning (ROCF). For patients impaired at baseline, a significant decline relative to controls observed for language (BNT, delayed recall of VPA)	High attrition and no control for drop-out in analysis. Time used as proxy of progression. No statement about controlling for motor speed in testing.
Kasper et al. (2016)	93 ALS and 73 controls, one follow up at six months and another at 3-6 months	No significant change, relative to controls, for task switching (TMT), short term memory (DS), cognitive inhibition (Stroop). Letter fluency showed a significant Time*Group effect but was not significant when age was added to model.	Sample size at each follow-up not reported. Adjustment for motor speed in assessment. Patient groups split into small groups which may affect statistical models. Time used as proxy of progression.
Burkhardt et al. (2017)	40 ALS (n_2 = 24, n_3 = 10) and 49 controls (n_2 = 21, n_3 = 0) three times at six month intervals	Practice effects in ECAS observed in control group. No change in ECAS cognition or Behaviour observed over time.	High attrition and lack of control group at time 3. Time used as proxy of progression. Practice effects in control group not controlled for in ALS.

Note. 5-PFT = 5-Point Fluency Test, AVLT = Auditory Verbal Learning Test, BVRT = Benton Visual recognition Test, COWAT = Controlled Oral Word Association Test, CWIT = Controlled Word Interference Test, DS = Digit Span, GNT = Graded Naming Test, JLO = Judgement of Line Orientation, PVLT = Peabody Verbal Learning Test, RAVLT = Rey Auditory Verbal Learning Task, RFT = Recurring Figures Test, ROCF = Rey-Osterrieth Complex Figure, ,RPM = Raven's Progressive Matrices, TAP = Test batterie zur Aufmerksamkeitsprüfung, VPA = Verbal Paired Associates, WCST = Wisconsin Card Sorting Test. n_2 = sample size at Time 2, n_3 = sample size at Time 3, n_4 = sample size at Time 4

1.11. Impact of cognitive and behaviour change

It is difficult to overstate the importance of understanding cognitive and behavioural status in ALS. Some clinicians may be reticent to subject patients to cognitive and behavioural assessments, however the potential benefits outweigh the perceived cost. The impact of physical symptoms associated with ALS has been widely demonstrated (Abdulla et al., 2014; Goldstein et al., 1998; Pagnini et al., 2010), yet, cognitive and behavioural symptoms appear to contribute uniquely to patients' and caregivers' quality of life, mood, and burden. Patients' quality of life has been associated with subjective cognitive lapses (Goldstein, Atkins, & Leigh, 2002). However, it may be behavioural symptoms that most impacts caregiver burden (Andrews, Pavlis, Staios, & Fisher, 2017; Chiò et al., 2010; Tremolizzo et al., 2016), quality of life and depression (Chiò, 2010), activities of daily living (Mioshi, Lillo, Kiernan, & Hodges, 2012), and relationship intimacy (Goldstein et al., 1998). In a survey of ALS caregivers, Lillo, Mioshi, and Hodges (2012b) found that 48% of carers experienced high levels of burden, and that abnormal behaviour and caregiver stress, not physical symptoms, significantly predicted this. Recently, in a relatively large cohort of 84 patients and caregiver dyads, the impact of cognition and behaviour on caregiver burden was explored. In this study, caregiver burden was significantly associated with patients' behaviour, even after controlling for severity of functional disability (Tremolizzo et al., 2016).

While the psychological impact on caregivers and people with ALS is sufficiently meaningful to justify knowing a patients' cognitive and behavioural status, the impact of such symptoms on disease course has recently been elucidated. In 2005, Olney et al. found that those with ALS and comorbid FTD

were less compliant with respiratory and nutritional interventions. Rates of non-compliance in ALS-FTD patients were twice that of ALS without comorbid dementia. Additionally, Chiò et al. (2012) found that while ALS cases with and without behavioural symptoms showed similar rates of nutritional and respiratory intervention uptake, patients with behavioural symptoms survived for shorter periods suggestive of poor treatment compliance. Martin et al. (2014) report that patients with a higher level of intellectual functioning were significantly more likely to accept respiratory and nutritional interventions.

Futhermore, Stukovnik et al. (2010) found that people with ALS were significantly less able than a control group in medication scheduling task. When asked to correctly and safely schedule a day's medication use, patients were less able to schedule pills at the correct time, and made more errors and omissions. This was despite spending a similar amount of time completing the task, making similar number of steps to completion, and viewing the instructions a similar amount of times as the control group. While these results are by no means conclusive, they highlight the potential impact that cognitive impairment can have on intervention compliance. Yet, some of the most notable findings regarding the impact of cognition and behaviour in ALS concerns survival. Behavioural change, particularly apathy (Caga et al., 2016), and cognitive change, particularly executive dysfunction (Elamin et al., 2011), have shown to be negative prognostic indicators in ALS, with significant survival time reduction of approximately one year (Chiò et al., 2012; Elamin et al., 2011; Gordon et al., 2010b; Gordon et al., 2011; Hu et al., 2013).

1.12. Assessment of cognition in ALS

As has been demonstrated, cognitive and behavioural symptoms are common in ALS. These symptoms can impact caregiver and patients' psychological wellbeing, medical decision making, patients' ability to engage with interventions, and have a negative prognostic effect on survival. Recently published guidelines on the assessment and management of patients with MND have emphasised the need for timely assessment of cognitive and behavioural symptoms as part of a multidisciplinary team (NICE, 2016). These guidelines highlight the impact that cognitive and behavioural status can have on issues of capacity, patient management, and care planning. Important factors should be considered in the assessment of neuropsychological status in ALS, namely, assessment factors and disease factors.

Assessment factors (practice effects): An important factor to consider is that of learning/practice effects that pervade neuropsychological testing. This occurs when a person is administered the same or very similar tests more than once. Performance can improve, not due to an increase in cognitive ability, but because the individual has become familiar with the test or the testing environment. Practice effects are worse for younger and more educated individuals (Calamia, Markon, & Tranel, 2012), for shorter durations between testing (Bartels, Wegrzyn, Wiedl, Ackermann, & Ehrenreich, 2010; Benedict, 2005), and are worse for tests that have a novel learning component. For example, some research has suggested that practice effects can persist in the Wisconsin Card Sorting Test for up to 7 years (Calamia et al., 2012). Not accounting for this improvement may

lead to the false belief that the patient is improving, or it may mask a decline if present.

Practice effects can, in some situations, be accounted for statistically, for instance, in the inclusion of control groups in statistical models. Other methods to control for practice effects are in using reliable change indices (Jacobson & Truax, 1991). These indices determine whether an observed change between testing sessions is statistically meaningful. Regression models (both univariate and multivariate) can also be used to generate predicted scores, which can then be compared to an individual's actual score (Temkin et al., 1999). However, statistical approaches may not always be appropriate, or the best method available. A common alternate method of accounting for practice effects is in the use of alternate forms. Alternate forms of a test are those in which multiple versions of the same test exist which measure the same outcome, in the same way, with similar levels of difficulty. For example, alternate forms of the Trail Making Test have been developed in which the placement of number and letters differ between forms such that the quantity of items to connect and their distances are the same (Wagner, Helmreich, Dahmen, Lieb, & Tadíc, 2011). Other common neuropsychological tests with alternate forms include the Rivermead Behavioural Memory Test (Wilson et al., 2008), Repeatable Battery for the Assessment of Neuropsychological Status (Randolph, 1998), and Montreal Cognitive Assessment (see Costa et al., 2012b).

Disease factors: Many neuropsychological assessment tools and experimental tasks rely on intact motor functioning, for instance, through timed or time-limited tests, or reaction speeds. Given that ALS is predominantly a disease of the brain's

motor system, it is surprising that research continues to be conducted without fully accounting for physical disability (e.g., Lepow et al., 2010; Machts et al., 2014; Pinkhardt et al., 2008; Rusina et al., 2010; Savage et al., 2014; Schreiber et al., 2005). Stukovnik et al. (2010) compared the test performance of ALS cases before and after correcting for motor disability. Before correcting, patients displayed high levels of impairment on numerous executive tasks (e.g., category fluency, Stroop Colour-Word Interference, Trail-Making), however, after correcting for motor speed, many tasks become non-significant. Not correcting for motor speed can lead to over-estimation of the cognitive difficulties of individuals.

As previously noted, respiratory status may be an important factor to consider when assessing cognitive abilities in ALS. Respiratory insufficiency has been shown to affect cognitive functioning, for example, in sleep apnoea (Findley et al., 1986; Lal, Strange, & Bachman, 2012), chronic obstructive pulmonary disease (Crews et al., 2001; Dodd, Getov, & Jones, 2010), and a relationship has similarly been suggested in ALS (Kim et al., 2007; Murphy et al., 2016; Newsom-Davis et al., 2001; Piepers et al., 2006). Therefore, careful consideration should be made as to how a patient's respiratory function may affect performance.

1.12.1 Cognitive Assessment tools

While extensive neuropsychological evaluations are considered the gold standard for assessment, they are burdensome to patients and require qualified clinical neuropsychologists. Brief assessments exist that can be administered by non-specialist healthcare professionals. Yet, these tools often assume intact motor functioning, and are not designed to measure the heterogeneous profile of

cognitive change in ALS. In recent years, several ALS-specific tools have been created to assess the cognitive and behavioural status of patients with MND. These tools can be informative for clinical practice, for research, and to determine whether a more extensive neuropsychological investigation is warranted. While several screening batteries have been suggested (see Table 1.6 for summary), the most relevant general screening instruments are the Edinburgh Cognitive and Behaviours ALS Screen (ECAS) and the ALS Cognitive Behavioural Screen (ALS-CBS), both of which include measures of cognition and behaviour. Both tools were designed specifically for ALS and can be used by any suitable healthcare professional. Recently updated ALS consensus guidelines suggest that all people with ALS be assessed using the ECAS or ALS-CBS (Strong et al., 2017).

Table 1.6. Cognitive Screening instruments

Name	Time Taken	Description	Strengths	Weaknesses
Penn State Screen Exam (Flaherty-Craig et al., 2006; 2009)	20 mins	A cognitive screen including measures of executive functions, language, visuospatial, fluency, and memory.	Revised adjusted for motor disability (Flaherty-Craig et al., 2009). Measures multiple areas of cognition. May be useful in detecting language variants of FTD.	Not formally validated. Expensive to use. Originally designed for other neurological disorders. Includes behaviour screen unadjusted for motor impairment.
Montreal Cognitive Assessment (Nasreddine et al., 2005)	15 min	A cognitive screen measuring visuospatial, executive, attention, language, memory, orientation.	Freely available. Alternate versions allow for repeat testing, and additionally has a 'mini form'. Measures multiple areas of cognition. Has been validated in numerous diseases and available in dozens of languages (see www.mocatest.org).	Not designed for ALS and relies on intact motor function, adaptations may be possible however (Osborne, Sekhon, Johnston, & Kalra, 2014). No behaviour measurement included.
Frontal Assessment Battery (Dubois, et al., 2000)	5-10 mins	A cognitive screen measuring executive functions, fluency, and motor programming.	Well validated for measuring frontal-executive functions.	Only measures executive functions. Not suitable for patients with motor disability (Raaphorst et al., 2013). No behaviour screen included.

ALS-Cognitive Behavioural Screen (*Cognitive section)* (Woolley, et al., 2010)	10 minutes	A cognitive and behavioural screen measuring executive functions, fluency, and attention	Very brief and most tasks independent of motor speed. Spanish version available (Turon-Sans et al., 2016). Good accuracy in detecting FTD (Woolley et al., 2010). Available freely. Formally validated in ALS (Woolley et al., 2010). Includes behaviour screen (See Table 1.7).	Primarily measures executive functions and does not address the heterogeneity of cognitive impairment. Fluency task does not adjust for motor speed. Limited ability to detect mild cognitive impairments (Woolley et al., 2010). Limited range of scores and presence of ceiling effects (Woolley et al., 2010)
ALS Brief Cognitive Assessment (Hu et al., 2013)	~5 mins	A 5-item cognitive and behavioural tool measuring executive functioning, fluency, and FTD behaviours.	Good accuracy for detecting FTD. Extremely brief.	Designed for other neurological populations. Not good at detecting mild cognitive impairment. Only measures executive functions. Does not control for motor speed.
Edinburgh Cognitive and Behavioural ALS Screen (Cognitive Section) (Abrahams et al., 2014)	15-20 mins	A cognitive and behavioural screen measuring executive functions, social cognition, language, visuospatial, and memory.	Measures multiple domains of cognition. Only tool to include social cognition. Available in 22 languages. All tasks adjusted for, or independent of motor speed. Available freely. Formally validated in ALS (Niven et al., 2015). Includes behaviour screen	Ceiling effects present in language and visuospatial subtests.

			(See Table 1.7). Available from ecas.psy.ed.ac.uk.	
UCSF Brief Screening Battery (Murphy et al., 2015)	40 mins	A combination of the ALS-CBS (Woolley et al., 2010), Abrahams' verbal fluency test (Abrahams, 2000), and an ALS version of the FBI administered to caregiver.	Same strengths as the ALS-CBS but combines a motor-independent measure of fluency with the ALS-CBS. Includes behaviour measure (ALS-FBI; Table 1.7). Improves predictive ability of ALS-CBS (Murphy et al., 2015). Includes a behaviour screen.	Does not account for cognitive heterogeneity. Considerably longer than the ALS-CBS.

1.12.1.1 ECAS

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) is a multi-domain cognitive and behavioural measure specifically designed for ALS (Abrahams et al., 2014; ecas.psy.ed.ac.uk). It contains 15 subtests divided into those functions most commonly impaired in ALS (ALS-Specific functions), and those less commonly associated with ALS (ALS Non-Specific functions). ALS-Specific functions include measures of executive ability, including working memory (reverse digit span), task switching (oral trail-making), inhibitory control (sentence completion), and social cognition (judgement of preference). Due to its sensitivity to detecting impairment in ALS, verbal fluency is measured as its own domain. Adapted for motor impairment by calculation of the verbal fluency index (Abrahams et al., 2000), the ECAS fluency task requires the free generation of 'S' words, and the restricted generation of 4-letter 'T' words (see section 1.6.2). Language functions are measured using tasks of confrontation naming, comprehension, and spelling. All tasks are designed to tap both noun and verb knowledge thereby accounting for the specific verb-deficit suggested in ALS. ALS Non-Specific tasks are those of memory (involving the immediate and delayed recall and recognition of a prose story), and visuospatial functions (including dot counting, cube counting, and number location).

All subtests of the ECAS can be adapted to the motor ability of the patient, in that responses can be given orally, verbally, or using assistive technology. The ECAS has been validated against a full neuropsychological battery and shows good sensitivity and specificity to cognitive impairment in Scottish (Niven et al., 2015), German and German-Swiss (Loose et al., 2016; Lulé et al., 2015), Italian (Poletti et al., 2016), Irish (Pinto-Grau et al., 2017), Chinese (Ye et al., 2016)

populations, and is available in Spanish (Mora et al., 2018). The ECAS possesses good convergent validity with other screening tools, for example, the Montreal Cognitive Assessment (Lulé et al., 2015; Poletti et al., 2016) and Frontal Assessment Battery (Poletti et al., 2016). In addition to its motor-free design, administration of the ECAS is possible in cases of severe motor disability where, by comparison, not all patients could complete the Montreal Cognitive Assessment and the Frontal Assessment Battery (Burkhardt, Neuwirth, & Webber, 2017; Lulé et al., 2015). The ECAS has additionally been adapted for eye-tracking and early results suggest it may be useful in the assessment of end-stage disease (Keller et al., 2017).

1.12.1.2. ALS-CBS

The ALS Cognitive Behavioural Screen (ALS-CBS; Woolley et al., 2010) is a short cognitive and behavioural screen specifically designed for ALS. It includes brief measures of attention (following commands, mental addition, eye movements), concentration/working memory (backward digit span test), tracking/monitoring (saying the months backward, reciting the alphabet, oral trail-making test), word initiation and fluency (letter fluency for letter 'F'). The ALS-CBS additionally includes a behaviour questionnaire addressing an extensive list of behaviours, including apathy, inhibition, empathy, emotional control, frustration tolerance, cognitive flexibility, insight, judgement, food preferences, decision making, and language. It has been validated against a full neuropsychological battery, with good sensitivity and specificity for detecting FTD; however, it is unable to distinguish mild cognitive impairment from FTD (Woolley et al., 2010). It has been validated in Brazilian Portuguese (Branco et al., 2017) and is available in Spanish

(Turon-Sans et al., 2016). The ALS-CBS benefits from being brief and can be utilised by any health care professional, as with the ECAS. While the ALS-CBS benefits from being largely independent of motor functioning, its most sensitive subtest, the verbal fluency test, is not adjusted for motor speed. While participants are able to speak, write, or use assistive communication devises, it does not adjust for the different lengths of time these methods take, nor for slowed motor speed.

The ALS-CBS has recently been incorporated into the UCSF Screening Exam (Murphy, Ahmed, & Lomen-Hoerth, 2015) which includes a separate measure of the Abrahams et al. (2000) fluency test adjusted for motor speed. While the ALS-CBS primarily measures executive functioning, and does not directly measure language, memory, or visuospatial functioning, the expanded UCSF Screening Exam includes an expanded ALS-specific behavioural measurement (ALS-FBI). A modified version of the UCSF Screening exam was proposed for utility in telephone administration. The ALS-CBS portion of the UCSF showed similarities between telephone and in-person testing. However, results suggest that the telephone-administered fluency components and the ALS-FBI screen are not equivalent to in-person testing (Christodoulou et al., 2016).

1.13. Assessment of behaviour in ALS

While ALS and FTD are now understood to be overlapping conditions, behavioural symptoms are largely mild in non-demented ALS (Raaphhorst et al., 2012a). As such, symptoms may go unnoticed, in part due to the lack of objective specificity in behavioural assessments. The culture and background of the

individual may mediate whether behaviours are considered abnormal. Moreover, the prevalence of mild ALS-FTD type behaviours in the general population has not been established. Common behaviours in FTD, such as apathy, hoarding, and disinhibition have been found in healthy ageing (Brodaty, Altendorf, Withall, & Sachdev, 2010; Esposito et al., 2014; Marx & Cohen-Mansfield, 2003; Morales-Vives & Vigil-Colet, 2012). This means that true prevalence of pathological behaviours is not fully known. Caregivers in Grossman et al. (2007) study reported that 11% and 20% of patients exhibited apathy and disinhibition prior to the onset of ALS, and as such, behavioural symptoms may manifest before physical symptoms (Mioshi, et al., 2014a).

Methods of behavioural assessment are inherently less specific and objective than those of cognition. Behaviours may be *symptomatic* or *reactionary* to the disease, for example, a person with ALS may exhibit apathy which may be a symptom of ALS, or a psychological reaction to the burden of the disease. Most behavioural assessments rely on information provided by a third party, a so-called informant. While this will often be the patient's spouse, this is not always possible. Assessment tools of behaviour that are currently available usually aim to diagnose overall dementia-related behaviour, rather than profiling specific behaviours such as apathy, disinhibition, or stereotypic behaviours. As such, their clinical utility can be limited. Moreover, many measures of behaviour used with ALS were not originally designed for a patient population with physical disability. As such, questions that seemingly measure a behaviour may be affected more so by an individual's motor disability.

1.13.1. Behavioural Assessment Tools

Behavioural assessment can be subjective, and it can be difficult to determine what constitutes abnormality. Generally, abnormal behaviours are those which represent a change from the individuals previous functioning or are considered out of place within the individual's unique context. Both questionnaires and interviews have been utilised as methods of assessment behaviour change in ALS. Additionally, many behaviour screens only provide information on overall behavioural dysfunction, and do not allow for the detection of specific behaviour manifestations. Questionnaire-based assessments reduce subjectivity to a degree but also result in a loss of the nuanced and variable presentations that behavioural symptoms can have. Common behaviour measurements used in ALS research are summarised in Table 1.7. Disease-specific tools have been published in recent years that attempt to overcome the possible confound of physical disability. The MiND-B, the ALS-FTD-Questionnaire, the Frontal Behavioural Inventory (ALS), ALS-CBS (behaviour screen), and the Beaumont Behaviour Inventory (BBI) are questionnaire-based measures of overall behavioural symptomatology, while the ECAS (behaviour screen) is interview based and designed to detect specific behavioural features.

Table 1.7. Behavioural screening instruments

Name	Time Taken	Description	Strengths	Weaknesses
ALS-FTD-Q (Raaphorst, Beeldman, Schmand, et al., 2012b)	5-10 mins	25 item behaviour questionnaire including questions of emotional lability and subjective cognitive functioning.	Based on systematic review and therefore likely to capture many of the common behaviours. Initial results of validation are promising. Takes frequency and severity of behaviours into account. Provides clinical cut-offs. Free to use. Independent of motor function.	Only validated in Dutch population. Does not provide information on individual behaviours. Is restricted to behaviours observed currently or over past month.
MiND-B (Mioshi, et al., 2014b)	5 mins	9 item caregiver questionnaire measuring apathy, disinhibition, and stereotypic behaviours.	Very brief and available freely. Data driven. Independent of motor function. Provides clinical cut-offs for presence of behaviour and subdomains.	Unable to differentiate severity of symptoms i.e., ALSbi to ALS-FTD (Hsieh et al., 2016; Mioshi, et al., 2014b). Only measures behaviour over previous month. Limited to three behaviours.

Frontal Behavioural Inventory-ALS (Murphy et al., 2015)	10 mins	The 24-item FBI was originally designed to measure behaviours associated with frontal lobe dysfunction (Kertesz et al., 1997). It has been adapted for motor disability in ALS. Information is provided by caregiver.	Instructions explicitly specify *changes* in behaviour not due to physical symptoms. Accounts for frequency of behaviour. Freely available.	No direct measure of symptom severity. Inconclusive results on its predictive ability. No cut-offs for impairment provided.
Edinburgh Cognitive and Behavioural ALS Screen (*Behaviour Section*) (Abrahams et al., 2014)	5-10 mins	Assesses 10 behaviour symptoms across 5 behaviour domains. Based on diagnostic criteria for FTD, including. Information is provided by caregiver.	Specifically designed for ALS. Provides opportunity to gather qualitative information about behaviours including frequency, severity, and time course. Based on FTD diagnostic criteria. Available freely. Includes cognitive screen.	Reliant on subjective judgement of clinician/researcher. Restricted to diagnostic criteria and may not fully reflect research findings of common behaviours in ALS.
ALS-CBS (*Behaviour section)* (Woolley, York, et al., 2010)	5 mins	Assesses overall behavioural involvement with 15 questions measuring multiple areas of behaviour. Four additional questions address depression, anxiety, emotional lability, and fatigue. Information is provided by caregiver.	Specifically designed for ALS and research driven. Behaviour screen is objective and accounts for symptom severity. Available freely. Includes cognitive screen.	Not detailed enough to measure specific behaviour domains. Does not cover behaviour domains included in FTD diagnostic criteria. Does not account for frequency of behaviours, and may be unreliable for behaviours that presented prior to onset of physical symptoms.

Neuropsychiatric Inventory (NPI) (Cummings et al., 1994)	10 mins	Developed for Alzheimer's disease, the NPI 10 or 12 (depending on version) measures aspects of behaviour and psychiatric symptoms.	Measures frequency, severity, and impact of symptoms. Quite detailed. Available in numerous languages. Short form version available (NPI-Q) (Kaufer et al., 2000).	Not specific to ALS and not independent of motor disability.
Frontal Systems Behaviour Scale (FrSBe) (Grace & Malloy, 2001)	10 mins	Originally developed for stroke patients (Grace & Malloy, 2001), the FrSBe is a 46-item scale assessing frontally-associated behaviours of apathy, executive dysfunction (functional aspects), and disinhibition.	Includes both carer and patient report forms. Can be used to estimate behaviour change from premorbid rates. Validated for use in FTD (Carvalho, Ready, Malloy, & Grace, 2013; Malloy, Tremont, Grace, & Frakey, 2007).	Not independent of motor functions. The FrSBe is costly to use. Limited to three behaviour domains. Too much focus of psychiatric symptoms which are uncommon in ALS.
Beaumont Behaviour Inventory (Elamin et al., 2017)	5-10 mins	41 item proxy-report questionnaire assessing behaviours noted in FTD diagnostic criteria, in addition to emotional lability, psychosis, and altered response to sensory stimuli.	Developed specifically for ALS incorporating multiple diagnostic criteria. Covers broad range of behaviours. Accounts for time and severity in ratings. Validated with large cohort.	Non-specific factor structure. No clear guidelines on measuring individual behavioural symptoms. Some question items are overly vague and the weightings of questions are unclear i.e., many more questions relating to perseveration than apathy.

1.13.1.1. ECAS Behaviour Screen

The ECAS includes a caregiver-interview behaviour screen measuring 10 symptoms of behaviour that combine into five dimensions, namely: disinhibition; apathy or inertia; loss of sympathy or empathy; perseverative; stereotyped; compulsive; or ritualistic behaviours; and hyperorality and altered food preferences. These domains are based on the revised diagnostic criteria for FTD (Rascovsky et al., 2011), which have shown good sensitivity and specificity to detecting FTD (Costa et al., 2013; Harris et al., 2013; Lamarre et al., 2013). The ECAS behaviour screen also measures psychotic symptoms less commonly seen in ALS cases (Strong et al., 2017). The ECAS behaviour screen benefits from its semi-structured interview design. It allows the freedom to probe the carer as to the frequency, severity, time-line, and qualitative nature of observed behaviours. Conversely, this adds variability in measurement due to interviewers' individual techniques.

1.13.1.2. ALS-Cognitive Behavioural Screen (ALS-CBS)

The behavioural section of the ALS-CBS is a brief 15-item carer questionnaire. Usefully, four additional questions address depression, anxiety, emotional lability, and fatigue. The ALS-CBS was specifically designed for ALS and as such, the behaviour screen is not dependent on motor function. However, as with other questionnaire-style tools, it cannot provide information on specific behaviours, does not account for frequency of behaviours, and specifies that behaviours should develop after motor symptom onset. Currently the ALS-CBS has

demonstrable ability to detect FTD, however, is has poor discriminant ability to differentiate mild behaviour change from FTD (Woolley et al., 2010).

1.13.1.3. Frontal Behavioural Inventory ALS Version (FBI-ALS)

The Frontal Behavioural Assessment was designed to measure frontally-mediated behavioural symptoms (Kertesz, Davidson, & Fox, 1997). It has been shown to have good predictive ability from differentiating FTD from other forms of dementia (Kertesz, Nadkarni, Davidson, & Thomas, 2000; Milan et al., 2008; Slachevsky et al., 2004). While it has been previously used to measure behaviour in ALS (Flaherty-Craig et al., 2009; Gordon et al., 2007; Hu et al., 2013), the original FBI contains questions that may be exaggerated by motor disability e.g., “Does s/he take as much care of his/her personal hygiene and appearance as usual”, or “does s/he neglect to wash or change his/her underwear?”. Murphy et al. (2015) has recently adapted the FBI to measure *changes* in behaviour, frequency of behaviour, and account for motor disability e.g., “When you think about those personal hygiene activities that they can complete on their own, does s/he neglect to initiate grooming or personal care activities as compared with their behaviour in the past?”. While the FBI-ALS is promising, and has recently been used in a large multi-centre research study (Murphy et al., 2016), its validity has not been fully established. The validity of the FBI-ALS has only been measured in a small sample of 24 patients, and was related to other measures of behaviour (the ALS-CBS behaviour scale, and the FrSBe) inconsistently. Additionally, cut-offs are not provided for determining behavioural impairment (Murphy et al., 2015). Further validation research is required to determine its research and clinical utility in ALS.

1.13.1.4. The Motor Neuron Disease Behaviour Scale (MiND-B)

The MiND-B is a brief data-driven tool derived from the Cambridge Behavioural Inventory (Mioshi, et al., 2014b; Wear et al., 2008). The MiND-B consists of 9 questions measuring levels of apathy, disinhibition, and stereotyped behaviour. The MiND-B was designed to detect behavioural impairment and benefits from providing individual domain-specific clinical cut-offs. In a recent study of 70 ALS patients, the MiND-B demonstrated good discriminant validity in detecting behavioural change. However, due to the variability present in behaviour scores of patients with ALS-FTD, the MiND-B was not able to discriminate between ALS-FTD and ALS with mild behaviour changes (Hsieh et al., 2016).

1.13.1.5. The ALS-Frontotemporal Dementia-Questionnaire (ALS-FTD-Q)

The ALS-FTD-Q is a 25-item caregiver questionnaire providing an overall behavioural symptomatology score, in addition to the frequency or severity of the symptoms. Questions include the domains of apathy, irritability, disinhibition, emotional lability, and altered food preferences. This scale was developed following a systematic search of behaviour symptoms in ALS (Raaphorst et al., 2012b). It has good validity and reliability and correlates well to the FrSBe (Raaphorst et al., 2012b). The ALS-FTD-Q is available in 9 languages, but has currently only been validated in Dutch, and recently Japanese (Watanabe et al., 2016). The cut-offs for this scale provide distinctions between mild behavioural symptoms and more severe symptoms (ALS-FTD), however, it does not provide clinically relevant measures of any individual behaviour. Further research is required to establish its transferability to English speaking audiences.

1.13.1.6. The Beaumont Behavioural Inventory (BBI)

The Beaumont Behaviour Inventory (BBI) is the most recently published behavioural assessment (Elamin et al., 2017). The questionnaire is based on multiple diagnostic criteria for FTD including the Neary and Rascovsky criteria. Questions cover the domains of apathy, disinhibition, loss of empathy and sympathy, perseveration, altered food behaviour, utilisation behaviour, and psychosis. Ratings of the BBI incorporate gross timelines (last 10 years and since onset of MND) and severity. The BBI possesses good sensitivity and specificity against the FrSBe for both mild behavioural impairment and FTD (Elamin et al., 2017). Burke et al., (2017) suggests that individual behaviour domains can be extracted from the BBI, however, no guidelines are provided which explain how this is achieved. Additionally, factor analysis of the BBI revealed non-specific groupings such that multiple behaviours types fall into one factor. As such, the structure and clinical utility of the BBI remain to be established.

1.14. Cognitive and behaviour screening summary

While classification systems describing patients as ALSci, ALSbi, or ALS-FTD may be useful for research purposes, the translation into clinical practice has not been evaluated. Providing indication that a patient may have a general cognitive or behavioural impairment may not provide the necessary detail to formulate additional support, or adjust care management. Additionally, focusing on cognition and behaviour as a unitary concept runs the risk of missing out patients whose impairment may be limited to one domain. An understanding as to the

individual cognitive and behavioural profile which is domain specific is more informative. Brevity may be important in a busy clinic environment, but the impact that non-motor symptoms can have warrants a review of how important such symptoms are viewed. To truly provide holistic and individualised care, time must be spent establishing the current cognitive and behavioural status of a patient so that the necessary support systems can be put in place.

In terms of cognitive assessment, full neuropsychological batteries are the gold standard. However, such an exercise is time consuming and burdensome for patients, and is therefore inappropriate for all cases of ALS. Fortunately, validated tools specific to ALS are available which provide the opportunity to provide cognitive assessment as standard practice. The ECAS and the ALS-CBS are the most widely recognised screening tools in ALS, providing measures of both cognition and behaviour. While the ALS-CBS benefits from a greater brevity compared to the ECAS, it is limited to assessing executive functioning. Given the growing evidence of language impairment and, to a lesser degree, memory involvement, broad screening tools such as the ECAS provide more comprehensive and clinically useful information. The ECAS, while longer than the ALS-CBS, takes only 20 minutes to administer and covers a broader range of cognitive functions. The ECAS is also available and validated in considerably more populations compared to the ALS-CBS and can detect mild cognitive impairment, whereas the ALS-CBS currently cannot. Additionally, the ALS-CBS is not entirely motor independent in that the verbal fluency task relies on motor speed. Though the ALS-CBS has been incorporated into the UCSF Brief Screening Battery, this battery takes approximately 40 minutes to administer

undermining the goal of clinical screening tools. As such, the ECAS is currently the best option for cognitive screening in ALS.

Assessment of behaviour in ALS benefits from a broader range of tools available. However, the quality of these tools remains to be established fully. Questionnaire based-tools attempt to reduce behavioural features, which are qualitative, to quantitative scores. Additionally, most do not address important factors, such as behavioural frequency, severity, whether the behaviour represents a change from premorbid functioning, or confounding variables such as motor disability. Unfortunately, behaviour screening tools have also lacked appropriate validation against clinical diagnosis or other standardised measures. The ECAS can detect mild behaviour change in addition to possible FTD when the consensus guidelines are applied (Strong et al., 2017). As with the cognitive screen, the ALS-CBS cannot differentially detect milder forms of behavioural impairment which are more common than full-blown FTD in ALS. The MiND-B was an important step forward in adapting a comprehensive behaviour tool for ALS. The MiND-B demonstrated good discriminant ability in detected FTD, however, as with the ALS-CBS it could not detect milder behavioural changes. Additionally, the MiND-B does not include measures of altered eating behaviours or loss of sympathy or empathy which are relatively common in ALS. The ALS-FTD-Q is the only questionnaire-based behaviour screen that allows for the detection of mild behaviour changes. However, an English language version has yet to be validated. Finally, the BBI while promising, is inconsistent as to the constructs being measured and whether it has the power to detect specific behaviour domains.

As such, the ECAS is the only behaviour measure which allows for the detailed exploration of behaviours common in FTD. Benefiting from its interview basis, the ECAS behaviour interview allows for the examination of specific behaviours in terms of frequency, severity, whether the behaviour represents a decline, and to tease apart the confounding effects of motor impairment. While a limitation may be that the ECAS requires clinical interpretation to determine the presence or absence of a behaviour, the breath of information gained outweighs this.

1.15. General Aims

It is now established that cognitive and behavioural impairment are common features of ALS, with ALS and FTD demonstrating considerable overlap. Specifically, executive functioning, language, fluency, and social cognition are commonly affected in ALS, while apathy is the most frequently reported behavioural feature. However, despite these advances, questions remain.

Associations between neuropsychological impairment and clinical disease variables have been proposed, but results are inconsistent. Additionally, whether neuropsychological impairment worsens over the course of the disease in ALS has yet to be established. Cross-sectional and longitudinal research examining the relationship between disease severity, spread, and cognition are highly variable. Cross-sectional research has been limited using imprecise measures of disease severity (i.e., the ALSFRS). Longitudinal studies have similarly been limited by the use of time or the ALSFRS-R as a proxy of disease progression,

by poor statistical methods which do not account for attrition, and small sample sizes. Furthermore, the assessment of cognition and behaviour continues to be confounded by tools not suited for patients with motor disability, or the presence of practice effects in repeated assessment. Fortunately, ALS-Specific tools for measuring cognition (i.e., the ECAS, see section 1.12) and standardised measures of disease progression (the King's Clinical Staging System, see section 1.4.2) are now available. As such, the general aims of this study are to amalgamate advances in the assessment of cognition, behaviour, and disease progression to elucidate the evolution of neuropsychological symptoms over the course of ALS.

Aim 1: Develop, and validate, alternate forms of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) to accommodate repeated longitudinal assessment in ALS (Chapters 2 and 3).

To explore cognition and behaviour longitudinally, alternate forms of the ECAS will first be developed. The newly developed forms will be equivalent to the original ECAS in terms of the content, difficulty, administration, length, and semantic characteristics. The new forms will allow for the repeated assessment of cognition in ALS while controlling for practice effects common in cognitive assessment. Cut-off scores will be derived from healthy control data, in addition to metrics of reliable change. As such, these tools will useful to both researchers and clinicians in tracking changes over the course of the disease. These new forms will then be utilised to achieve Aims 2 and 3.

Aim 2: Explore how cognition and behaviour relate to clinical disease stage in ALS (Chapter 4).

Cross-sectionally, a cohort of ALS patients will be recruited from three research sites: Edinburgh, Dublin, and London. Assessment of cognition and behaviour will be conducted using the original ECAS form and compared against each patients' disease stage using the King's Clinical Staging System. This study will allow us to explore whether a patients' neuropsychological functioning is related to how advanced their disease is, and whether other clinical variables relate to neuropsychological symptoms.

Aim 3: Explore how cognitive and behavioural symptoms evolve over the course of the disease in ALS (Chapter 5).

Patients recruited from the three research sites will be followed up at clinical meaningful intervals. Patients' cognitive and behavioural functioning will be monitored longitudinally and as they transition through disease stages using the alternate forms of the ECAS. This will allow for the examination of longitudinal trajectories over time, how changes relate to one another and to clinical disease stage, and evaluate the presence of patient subgroups. Additionally, this study will also allow for the longitudinal validation of Aim 2.

Aim 4: Explore clinicians' attitudes and practices around cognitive and behavioural screening in ALS (Chapter 6).

It is currently unknown how clinicians think about cognitive and behavioural screening in ALS. This study will qualitatively explore clinicians' attitudes toward cognitive and behavioural assessment, their practices, and whether barriers exist in implementing screening programmes.

CHAPTER 2: ECAS A-B-C: Alternate forms of the Edinburgh Cognitive and Behavioural ALS Screen

Previous research of cognition in ALS has been limited owing to the use of assessment tools which are not appropriate for participants with motor weakness. This is of particular importance when examining how cognition evolves of the course of the disease due to the progressive nature of physical disability in ALS. The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was developed to overcome the limitations imposed by physical disability and provide a comprehensive and ALS Specific measure of neuropsychological functioning.

However, as with many cognitive assessment tools, the utility of the ECAS in monitoring cognition longitudinally is potentially limited by practice effects. To overcome the limitations imposed by practice effects, Chapter 2 describes the development of the ECAS alternate forms (ECAS-B and ECAS-C). The following chapter was published open access (CC-BY) in *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* (DOI: 10.1080/21678421.2017.1407793). Supplementary materials published with this article are available in Appendix II. Alternate versions of the ECAS and its guidelines are presented in Appendix V.

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RESEARCH ARTICLE

ECAS A-B-C: alternate forms of the Edinburgh Cognitive and Behavioural ALS Screen

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Abstract

Background: The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) is a short assessment by which neuropsychological symptoms can be detected and quantified in people with ALS. To avoid potential practice effects with repeated administration, here we present alternative versions of the ECAS suitable for measuring change over time. *Objective*: To develop two alternate versions of the ECAS: ECAS-B and ECAS-C. *Method*: One hundred and forty-nine healthy adult participants were recruited. Thirty participants completed a pilot study in developing the alternate versions. Two groups of 40 participants were administered the ECAS-B or ECAS-C and compared to published data of the original ECAS (ECAS-A) to determine equivalence. An additional 39 participants were administered the ECAS consecutively, either repeating the original version (ECAS-A-A-A) serially or the different versions (ECAS-A-B-C) to determine potential practice effects. Recordings of assessments were scored by a second researcher to determine inter-rater reliability. *Results*: No significant differences were found between versions (A, B, C) of the composite performance measures of ALS Specific, ALS Non-Specific, and ECAS Total scores. Repeated serial administration of ECAS-A (A-A-A) produced some practice effects for composite scores, whereas no such effects were found when alternate versions were administered serially (A-B-C). Exceptionally high intra-class correlations were found for all three versions of the ECAS suggesting a high degree of rater agreement. *Conclusion*: The newly developed alternate forms of the ECAS are both highly equitable to the original ECAS-A and enable avoidance of practice effects, thus supporting their use in measuring cognition and behaviour over time.

Keywords: *Cognition, behaviour, screen, ECAS, alternate forms, reliability*

Introduction

Up to 50% of patients with ALS will experience changes in cognition and/or behaviour. Considerable clinical (1,2), genetic (3), pathological (4), and neuropsychological data (2–5) have demonstrated that ALS and frontotemporal dementia (FTD) significantly overlap. The observed cognitive and behavioural changes in ALS parallel those observed in frontotemporal dementia, namely, deficits in executive functions, language functions, verbal fluency, and social cognition (6–9). Similarly, behavioural features of ALS include apathy, perseveration, and disinhibition (10–12). Despite this overlap, cognitive and behavioural symptoms in ALS do not always fall neatly into the three recognized FTD subtypes: behavioural variant FTD, non-fluent progressive aphasia and semantic dementia, raising the question whether ALS/FTD might be more than a simple juxtaposition on ALS and FTD (13). This underlines the

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importance of an ALS-appropriate cognitive and behavioural assessment.

However, the assessment of cognition in ALS has been historically difficult due to the ubiquitous requirement for intact motor functioning in neuropsychological assessment. The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) has been recently developed to overcome this issue (14). The ECAS has been designed to measure cognitive functions, unrestricted by physical disability (15), that are commonly affected in ALS (executive functioning, language functioning, and verbal fluency) in addition to functions less commonly affected (memory and visuospatial functions). Additionally, the ECAS includes a clinical caregiver behaviour interview based on diagnostic criteria for FTD (16). Although ECAS has been primarily designed for use in ALS, it may be useful in all patients in whom motor dysfunction might influence their performance on cognitive tests, e.g. Parkinsonism or paraplegia. The ECAS is a short screening tool designed with high clinical utility and is administrable by non-neuropsychological health care professionals. It has been validated against a comprehensive neuropsychological battery in Scottish (17), German/Swiss-German (15,18), Italian (19), Chinese (20), and Irish populations (21).

Given the brevity of the ECAS and its accommodation for physical disability, it may be suitable for measurement of changes in symptoms over the course of the disease. Cognitive dysfunction may have important implications for patient management, treatment fidelity, power of attorney, and end-of-life decision making (22–24). Behaviour change has been linked to increased carer burden (25,26) and shortened survival (27,28). As such, the accurate assessment of cognition and behaviour over time is of vital importance to meeting the needs of patients and their families. However, it has been well documented that the repeated administration of the same neuropsychological test can result in an improvement in performance (29). This improvement, termed practice effects, may result from 1) learning the content of test items, e.g., remembering the content of a prose story to be remembered; and 2) development of test-taking strategies (30,31). With regard to ALS, practice effects may mask subtle deteriorations in cognition, or exaggerate improvements due to intervention. Recently, Burkhardt et al. (2016) demonstrated the presence of practice effects with the ECAS whereby participants' performance significantly improved over serial assessments of six months (32).

A common method for overcoming practice effects is the development of alternate versions of a test in which elements of the test are changed while retaining characteristic features and level of difficulty (33). The aim of this study was to develop alternate forms of the ECAS to permit repeated assessment of cognitive functions in ALS over time, and for the accurate monitoring of cognitive and behavioural progression during the disease course. Specifically, this study aimed to: (1) present two alternate versions of the ECAS (ECAS-B and ECAS-C); (2) investigate the equivalency of the ECAS alternate forms to the original ECAS (ECAS-A); (3) investigate whether alternate forms of the ECAS reduce practice effects during serial administration compared to repeated administration of the original ECAS; and (4) investigate the inter-rater reliability of all three versions of the ECAS.

Methodology

Participants

One hundred and forty-nine healthy adults were recruited prospectively and matched by age, gender, and education to that of the original publication of the ECAS (14). Participants were representative of the demographic profile of ALS patients. Additionally, the previously published (retrospective) data on the ECAS ($n = 40$) were included in this study (14), resulting in a total sample size of 189 participants. Participants were free of current or past neurological or psychiatric conditions, reading/writing disabilities, and were not a blood relative of a person with ALS. Participants were recruited from a volunteer panel held by Edinburgh University, in addition to local charitable organizations and community noticeboards.

Development of the ECAS-B and ECAS-C

The ECAS cognitive screen consists of 15 subtests measuring five cognitive domains, namely: Language, Verbal Fluency, Executive (ALS-Specific) and Memory, Visuospatial (ALS Non-Specific) functions. To develop alternate versions of the ECAS cognitive screen, a pool of alternate stimuli was generated for each subtest and piloted on a sample of healthy adults. Stimuli selection and development is described in supplementary materials. Arrays of stimuli were carefully selected and formed into two alternate ECAS versions, the ECAS-B and the ECAS-C. Selection of stimuli was based on an item-by-item and group-level exploration of response accuracy, in addition to retaining semantic and linguistic characteristics present in ECAS-A. The ECAS A, B, and C and guidelines for usage are available on http://ecas.psy.ed.ac.uk.

Procedure

Participants were recruited into six consecutive groups across three study phases (Table 1). In phase 1, a pool of alternate stimuli was generated to produce two alternate forms of the ECAS (ECAS-B and ECAS-C) and were administered to a sample of

Table 1. Description and function of participant groups.

Phase	Function	Procedure	*n*
Phase 1: Pilot study	ECAS-B and ECAS-C formation	Administered array of possible stimuli	30
Phase 2: Establishing normative data	Establish normative data and equivalence of alternate forms	Administered ECAS-A	40
		Administered ECAS-B	40
		Administered ECAS-C	40
Phase 3: Exploring practice effects	Measure relative practice effects of administering same versus different ECAS forms	Administered ECAS-A serially	20
		Administered ECAS-A, ECAS-B, and ECAS-C sequentially	19

30 participants to broadly determine equivalence in performance between corresponding sets of items in these two versions. In phase 2, the ECAS-B and ECAS-C were administered to two prospectively recruited groups of 40 participants matched by age, gender, and education to the data of 40 healthy controls whose data were previously used to establish normative data for the ECAS-A (14).

In phase 3, an additional 39 participants were randomly assigned to one of two conditions. Participants were either administered the ECAS-A three times consecutively (A-A-A), or administered alternate forms of the ECAS (A-B-C). As practice effects have shown susceptibility to short retest intervals (e.g. see Calamia, Markon, & Tranel, 2012) and to maximize the possibility of detecting such effects, participants were administered the ECAS repeatedly during the same sitting. Phase 3 testing for each participant lasted approximately 50 min, limiting the possibility of fatigue. Between each ECAS administration for both groups, participants completed a 5-min visual-search distractor task or a 5-min rest to further reduce the possibility of fatigue. Additionally, all prospective participants were administered the Test of Premorbid Functioning (TOPF) as an estimate of Full-Scale IQ (FSIQ) (34).

The inter-rater reliability of all forms (A, B, and C) of the ECAS was additionally explored. A subset of participants consented to having their assessment session audio-recorded ($n = 94$). These audio recordings were then scored by a second rater, trained to administer and score the ECAS by the scale's authors (14). Both raters (RR and CC) were experienced in the administration and scoring of the ECAS. When audio recordings were unclear or given in written format, raw unscored paper forms were provided.

All participants provided informed written consent and this research was approved by the Psychology Research Ethics Committee of the University of Edinburgh.

Statistical analysis

Demographic data and estimated FSIQ were compared across groups using a χ^2 test for categorical data and one-way analysis of variance (ANOVA) for continuous data. For all analyses, when distributions or residuals violated statistical assumptions, power- or log-transformations were applied. When transformations failed to correct violations of test assumptions, non-parametric alternatives were used. Analyses were conducted using R 3.3.2. In all cases, alpha was set to 0.05.

To explore the equivalence of the ECAS-A, ECAS-B and ECAS-C forms, three analysis methods were employed on the scales' targeted domains (language, executive functioning, fluency, memory, visuospatial), as well as ALS-Specific, ALS Non-Specific, and ECAS Total scores. A one-way ANOVA or Kruskal-Wallis test was used to compare the alternate forms' means or medians (as appropriate). Kolmogorov-Smirnov tests were employed to compare the shape and spread of the distribution for ECAS-B and ECAS-C compared to ECAS-A. Standard null hypothesis significance testing does not directly assess the equivalence of data, but rather tests the evidence against the null. As such, the one-way ANOVA and Kolmogorov-Smirnov tests were employed to assess whether means and distribution of scores on the ECAS alternate forms significantly differ. Consequently, a Bayesian ANOVA was employed to directly test the null hypothesis and examine the probability that the ECAS alternate forms are the same. Bayes factors for the null hypothesis were calculated using medium prior of 0.7. Due to significant rates of ceiling effects in the Language and Visuospatial domains of the ECAS, Fisher's exact test for count data was used.

Possible practice effects of using ECAS A-A-A versus ECAS A-B-C were explored using a mixed effects model with Time and Group (A-A-A versus A-B-C) and a random intercept and slope fitted for each participant. To explore the differential impact of Group the interaction term (Time*Group) was added to the model. p values were obtained for the mixed effect model by likelihood ratio tests of the full model (Time*Group) against a reduced model without the interaction term.

Finally, inter-rater reliability of all three forms of the ECAS was explored using intra-class correlation (ICC) to determine the degree of agreement between two independent raters. ICCs and their 95% confidence intervals were calculated based on

mean-rating, absolute-agreement, two-way random-effects models (35).

Results

ECAS B and ECAS C: Normative data and equivalency

Prospectively recruited participants ($n = 80$) were randomly assigned to one of two groups and matched by age, gender, and education to a third retrospectively collected group ($n = 40$). No significant differences were observed for background demographic data, nor for estimated FSIQ between the two prospectively recruited groups (Table 2).

Mean performance for each ECAS cognitive domain across alternate forms was similar (Table 3). Results of one-way ANOVAs, Kruskal-Wallis, and Kolmogorov Smirnov tests demonstrated no significant differences between forms in the domains of Fluency, Executive Functions, and Memory. Additionally, no significant differences were observed for the ALS Non-Specific, ALS Specific, and ECAS Total composite scores. Fisher's exact test for Language revealed no significant difference in the frequency of scores obtained ($p = 0.147$). Conversely, the Visuospatial domain was significantly different across ECAS versions ($p = 0.013$). This difference was, however, entirely driven by a larger proportion of participants for ECAS-B and ECAS-C making a single error (i.e. scoring 11 out of 12).

Thresholds for impairment for the alternate versions (ECAS-B and ECAS-C) demonstrate parity across all versions using both 2 standard deviations and the 95th percentile. Cut-offs for impairment are retained from ECAS-A for the ECAS-B and ECAS-C (Supplementary Table 2).

Table 2. Demographic characteristics of independent ECAS A, B, and C groups.

	ECAS-A ($n = 40$)	ECAS-B ($n = 40$)	ECAS-C ($n = 40$)	p
Age	59.20 ± 12.58	60.20 ± 15.32	58.52 ± 14.28	0.856
Gender (Male)	45%	45%	43%	0.967
Education (Years)	12.28 ± 2.52	13.84 ± 3.25	13.38 ± 3.25	0.086
TOPF*	–	106.51 ± 11.90	105.46 ± 9.81	0.670

*TOPF (Test of Premorbid Function) unavailable for retrospective data. Welch t-test applied.

Practice effects

Participants were randomly assigned to one of two conditions; the 'same' group received ECAS-A three times serially (A-A-A), while the 'different' group was administered ECAS-A followed by ECAS-B and ECAS-C (A-B-C). No significant differences were observed between groups in age, gender, and education (Table 4). One-way repeated analysis of variance for the ECAS A-A-A group demonstrated a significant improvement over time for ALS Specific ($F(2,38) = 5.68$, $p = 0.007$), ALS Non-Specific ($F(2,38) = 100.42$, $p < 0.001$), and ECAS Total Scores ($F(2,38) = 25.88$, $p < 0.001$) as displayed in Figure 1. Additionally, the executive and memory subdomains and the majority of their subtests demonstrated a significant improvement over time (See Supplementary Table 3). No significant differences were observed in ALS Specific, ALS Non-Specific, or ECAS Total Scores for participant in the ECAS A-B-C group, nor any cognitive subdomains or subtests.

A significant group difference was observed in baseline ECAS-A Total score ($t(36.72) = 3.03$, $p = 0.005$) with those in the ECAS A-B-C group performing better than the ECAS A-A-A. However, a six-point difference was observed between groups for estimated FSIQ. While this did not reach statistical significance, a linear regression model demonstrated a significant positive effect of IQ on ECAS Total Score ($F(1,34) = 13.67$, $p < 0.001$, $\beta = 0.449$) explaining 28.67% of the variance.

Table 4. Demographic characteristics of ECAS A-B-C (different) and ECAS A-A-A (same) groups.

	Different ($n = 19$)	Same ($n = 20$)	p
Age	55.00 ± 10.32	57.25 ± 12.67	0.546
Gender (Male)	57.89%	50%	0.863
Education (Years)	16.21 ± 2.52	15.53 ± 2.54	0.401
TOPF	113.19 ± 10.20	107.30 ± 10.63	0.099

TOPF = Test of Premorbid Functioning.

Table 3. Comparison of performance across independent groups for the ECAS A, B, and C.

Domain	ECAS-A	ECAS-B	ECAS-C	ANOVA	KS A-B	KS A-C	Bayes BF_{01}
Language	27.62 ± 0.70	27.18 ± 1.15	27.12 ± 0.99	–	–	–	–
Fluency	19.85 ± 2.50	19.70 ± 2.99	20.45 ± 3.09	0.190*	0.999	0.914	6.72
Executive Functions	40.48 ± 3.54	40.23 ± 4.05	39.77 ± 3.70	0.703	0.999	0.759	9.43
Memory	18.68 ± 2.73	18.62 ± 2.17	18.30 ± 3.21	0.906	0.573	0.914	10.52
Visuospatial	11.85 ± 0.48	11.45 ± 0.81	11.43 ± 0.90	–	–	–	–
ALS-Specific	87.95 ± 4.98	87.10 ± 5.77	87.35 ± 5.34	0.775	0.914	0.914	10.14
ALS Non-Specific	30.52 ± 2.96	30.07 ± 2.39	29.73 ± 3.62	0.519	0.164	0.759	7.09
ECAS Total	118.47 ± 6.64	117.17 ± 7.15	117.08 ± 7.12	0.610	0.164	0.573	8.34

*Kruskalskal-Wallis test. KS = Kolmogorov-Smirnov test. BF_{01} = Bayes factor for the null hypothesis. Due to ceiling effects, statistical analysis here was not appropriate for language and visuospatial functions.

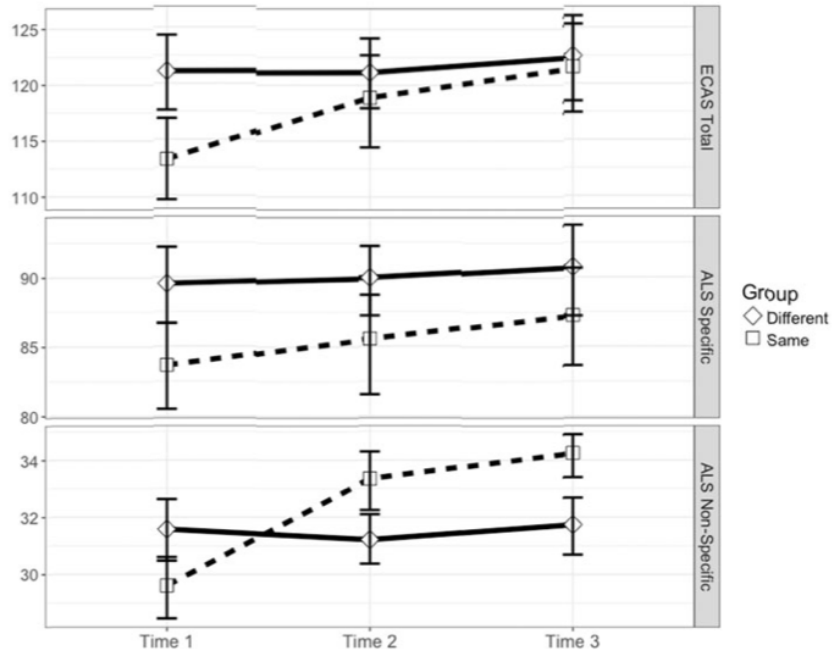

Figure 1. Comparison of practice effects using the same (A-A-A) versus different (A-B-C) versions of the ECAS.

Due to this small but significant difference in baseline performance between groups, a linear mixed effect model was fit. The addition of an interaction term (Group*Time; $b = 3.44$, $SE = 0.859$) significantly contributed to the fit of the ECAS Total model ($\chi^2(1) = 13.43$, $p < 0.001$). A similar significant Time*Group interaction was observed for ALS Non-Specific functions ($b = 2.25$, $SE = 0.341$, $p < 0.001$), but not for ALS Specific functions ($b = 1.20$, $SE = 0.77$, $p = 0.127$).

The effect of Time*Group was significant for ECAS Total and ALS Non-Specific functions, even accounting for a random intercept and slope for each participant (i.e. individual variation in baseline performance and rate of change), suggesting that the rate of improvement of using the ECAS-A serially is significantly greater than using the ECAS alternate forms.

Inter-rater reliability

Mean-rating, absolute-agreement, two-way random effects ICC models were generated for each cognitive domain and version of the ECAS. Across all versions of the ECAS and for all cognitive domains, inter-rater reliability was excellent ranging from 0.930 to 0.998. Supplementary Table 1 displays the respective ICC, 95% confidence intervals, and model statistics for each comparison; in all cases $p < 0.001$ indicated significant agreement between independent raters.

Discussion

The ECAS was developed to accurately assess cognitive functions in patients with ALS while controlling for motor disability. Not only has the ECAS shown high sensitivity and specificity to cognitive impairment against a full neuropsychological battery (17–21), it has high clinical utility in describing the nature of these impairments. Monitoring progression of cognitive and behavioural symptoms may have important implications for patient management, treatment, prognosis, end-of-life decision making, and caregiver burden (22–28). The purpose of this study was to develop alternate forms of the ECAS to facilitate repeated assessment and longitudinal monitoring of cognition and behaviour in patients with ALS. Particularly, the aims were to present and determine equivalency of two alternate forms of the ECAS (ECAS-B and ECAS-C) to the original ECAS-A, to investigate whether alternate forms of the ECAS reduce practice effects relative to the ECAS-A, and to investigate the inter-rater reliability of all three forms of the ECAS.

The findings in this study provide strong evidence that the newly developed ECAS-B and ECAS-C are equivalent to that of the original ECAS-A. Results of independent group analysis suggest that (1) performance on the alternate forms does not significantly differ from the original ECAS; and (2) there is strong evidence that the alternate forms come from the same distribution of scores. While a single significant difference was observed for the visuospatial domains of the ECAS, examination

of the score distribution revealed that this is due to ceiling effects and driven by a one- point difference in the alternate versions, therefore not affecting the equivalence of the alternate forms.

To establish the utility of the alternate forms in reducing practice effects, the ECAS-A was administered serially to a group of participants and compared to a separate group who were administered the alternate versions of the ECAS. Results of this study suggest significant practice effects exist for the ECAS-A when administered serially. This finding is in agreement with recent research demonstrating that the ECAS-A is susceptible to practice effects with repeated administration (32). The present study was designed to maximize the possible detection of practice effects as short intervals have been shown to exacerbate such an effect (29). However, no significant change in performance was detected over time when alternate versions of the ECAS were administered. Additionally, a significant Time by Group (i.e. time representing repeated assessment and group representing participants who received the same or different versions of the ECAS) interaction was observed when the ECAS A-A-A group was compared to the ECAS A-B-C group. The mixed effects model used in the analyses considered individual variability over time and baseline performance for each participant, suggesting that differences in practice effects were not due to individual variation. Rather, evidence herein suggests that the use of alternate versions of the ECAS is successful in reducing practice effects present in the repeated administration of the ECAS-A.

Cut-off scores, based on 2 standard deviations (SD) below the mean, for abnormality have previously been reported for the ECAS-A (14) and validated against a full neuropsychological battery (17). The present study demonstrated that the newly presented alternate versions are highly equivalent to the original ECAS. Examination of the cut-off scores for the alternate versions (ECAS-B and ECAS-C) demonstrate equality across all versions using two common methods (i.e. 2 standard deviations below the mean and the 95th percentile). For example, using a threshold of 2 SDs, the cut-offs for ALS-Specific functions is 77, 75, and 76 for versions A, B, and C, respectively. Similarly, cut-offs using the 95th percentile for ECAS Total scores are 105 for both ECAS-B and ECAS-C, where the published cut-off for ECAS-A is also 105. Given the lack of clinically meaningful differences between versions, the lack of observable practice effects, and similar cut-offs using two different methods, the cut-offs for the ECAS-A have been retained for the alternate versions and are displayed in Supplementary Table 2.

An additional goal of this study was to explore the inter-rater reliability of the ECAS and its alternate form. The administrations of the ECAS in this study were audio-recorded and scored by a second independent rater. Agreement for all cognitive domains and versions of the ECAS ranged between 0.930 and 0.998, providing evidence of exceptionally high agreement. While these findings are promising, one caveat here is that both raters had a background in psychology and were trained in the use of the ECAS by the scale's authors. Care should be taken in inferring generalisability in rater agreement between health care professionals with different professional backgrounds (e.g. nurses, neurologists). However, the two raters in this study (CC and RR) were highly experienced in administering the ECAS resulting in an excellent level of agreement. This highlights the benefit of appropriate training in the standardization of assessment and, as such, training is recommended for all health professionals using the ECAS.

The findings of this study provide strong evidence that the alternate versions of the ECAS are equitable to the original ECAS and allow for the longitudinal monitoring of cognitive function in individuals with ALS. However, some further research is required to explore how the alternate versions function over time. In this study, the alternate forms were presented in a fixed order (A-B-C) and for practical purposes this order is therefore recommended. While no evidence of order effects was found herein, future research may explore order effects using randomized presentation. Furthermore, reliable measures of change are needed to determine what change in performance is over and above normal variation and constitutes a significant improvement or decline in function. Methods such as the Reliable Change Index or regression based methods will in the future allow for this.

Ceiling effects were observed in all three versions of the ECAS for the language and visuospatial domains. While ceiling effects are common in neuropsychological tests, they limit the certainty with which equivalency can be assumed. It would be beneficial to explore the relative practice effects of using the same versus different ECAS versions in an ALS sample whom are less likely to approach ceiling.

Finally, future research may explore the effect of different testing intervals on repeated assessment. Testing intervals of 4, 6, and 12 months may be common within research and clinical practice and the effect of interval length should be explored in relation to reliability statistics of the ECAS alternate versions.

In conclusion, our findings suggest that the ECAS-B and ECAS-C are demonstrably equivalent to the original ECAS and provide the opportunity to monitor the longitudinal cognitive and behavioural profile of people with ALS longitudinally while controlling for practice effects both clinically and in research settings. Therefore, the neuropsychological

profile may be monitored over the course of the disease allowing clinicians to provide time-appropriate, accurate, and person-centred care services.

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Declaration of interest

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Supplementary material available online

In Chapter 2, the alternate forms of the ECAS (B and C) were found to be equivalent to the original ECAS-A. Not only were alternate forms shown to be equivalent, cut-off scores for impairment demonstrated substantial parity across versions. It was demonstrated that the repeated assessment of cognition over short test-retest intervals using version A resulted in practice effects, whereas no such result was observed when the alternate versions were used. Finally, inter-rater reliability of the three forms (A-B-C) were excellent. As such, the newly developed ECAS-B and ECAS-C are valuable for measuring the evolution of cognition longitudinally in ALS.

However, further investigations are required to validate their reliability over clinically meaningful time periods. Additionally, the interpretation of individual patients' change scores necessitates the calculation of reliability thresholds.

CHAPTER 3: Measuring reliable change in cognition using the Edinburgh Cognitive and Behavioural ALS Screen (ECAS)

In the previous chapter, it was shown that the ECAS-B and C overcame practice effects when administered in an experimental setting. However, ALS patients attending clinics will often return at approximately 3-6 month intervals. As such, it is important to validate the properties of the alternate forms across clinically meaningful times periods. Additionally, to improve the clinical utility of the ECAS-B and C, further investigation is required to accommodate the case-by-case interpretation of change over time.

Chapter 3 describes the establishment of reliable change scores for the ECAS alternate forms, and test-retest reliability across clinically relevant intervals. The following chapter was published open access (CC-BY) in *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* (DOI: 10.1080/21678421.2017.1407794). Supplementary materials published with this article are available in Appendix III.

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RESEARCH ARTICLE

Measuring reliable change in cognition using the Edinburgh Cognitive and Behavioural ALS Screen (ECAS)

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Abstract

Background: Cognitive impairment affects approximately 50% of people with amyotrophic lateral sclerosis (ALS). Research has indicated that impairment may worsen with disease progression. The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was designed to measure neuropsychological functioning in ALS, with its alternate forms (ECAS-A, B, and C) allowing for serial assessment over time. *Objective*: The aim of the present study was to establish reliable change scores for the alternate forms of the ECAS, and to explore practice effects and test-retest reliability of the ECAS's alternate forms. *Method*: Eighty healthy participants were recruited, with 57 completing two and 51 completing three assessments. Participants were administered alternate versions of the ECAS serially (A-B-C) at four-month intervals. Intra-class correlation analysis was employed to explore test-retest reliability, while analysis of variance was used to examine the presence of practice effects. Reliable change indices (RCI) and regression-based methods were utilized to establish change scores for the ECAS alternate forms. *Results*: Test-retest reliability was excellent for ALS Specific, ALS Non-Specific, and ECAS Total scores of the combined ECAS A, B, and C (all $>.90$). No significant practice effects were observed over the three testing sessions. RCI and regression-based methods produced similar change scores. *Conclusion*: The alternate forms of the ECAS possess excellent test-retest reliability in a healthy control sample, with no significant practice effects. The use of conservative RCI scores is recommended. Therefore, a change of ≥ 8, ≥ 4, and ≥ 9 for ALS Specific, ALS Non-Specific, and ECAS Total score is required for reliable change.

Keywords: *Cognition, ECAS, alternate forms, test reliability, practice*

Introduction

Cognitive and behavioural symptoms affect approximately 50% of patients with amyotrophic lateral sclerosis (ALS), of whom 15% develop FTD (frontotemporal dementia) and the two form a spectrum disease. Executive dysfunction, language dysfunction, and social cognitive deficits are commonly reported (1–3). The presence of cognitive and behavioural symptoms in ALS can precede motor symptoms (4), have been associated with reduced survival (5,6), disengagement with life prolonging interventions (7), and increased caregiver burden (8,9). Neuropsychological status has additional implications for end-of-life care planning, capacity to consent, and powers of attorney (2). Thus, timely and accurate knowledge of patients' cognitive and behavioural status is vital for providing person-centred care.

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The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was developed to offer a comprehensive screening tool to assess the cognitive and behavioural status of patients with ALS (10). The ECAS has been validated against full neuropsychological test batteries (11–16) and was designed specifically for patients with ALS in that it accommodates motor disability.

Cognitive decline over the course of the disease (17), or in response to specific disease factors such as respiratory insufficiency (18), has been suggested and it is consequently important to monitor progression of cognitive symptoms. Howevert, repeated assessment using neuropsychological tests may result in improvement due to practice effects, i.e. improvement in performance due to learning test content, or test-taking strategies. For clinicians, it can be difficult to interpret whether an observed difference in test performance is due to true change in the patient's situation (recovery or decline) or extraneous factors. Measurement error, regression to the mean, and practice effects can produce or exaggerate changes in performance between testing sessions. Furthermore, demographic factors such as age, education level, and baseline performance can influence change in scores between testing sessions, and therefore, obscure a patient's true performance variation (19). With regard to the ECAS, practice effects have been demonstrated with healthy controls in the executive, language, and memory domains over six months, when using version A for repeat assessments (20).

Recently, alternate forms of the ECAS have been developed to accommodate the repeated assessment of patients with ALS (21). The alternate forms of the ECAS (the ECAS-B and ECAS-C) were designed to retain the construct characteristics and level of difficulty of the original ECAS-A while reducing potential practice effects. The ECAS-B and C have shown to be equivalent to the original ECAS-A, and resistant to practice effects from repeated administration (21). It has yet to be determined what can be regarded as a meaningful change on a case-by-case basis. Numerous methods have been proposed to support the interpretation of change scores on neuropsychological tests. Most notably, clinicians have utilized reliable change indices (RCI) and regression-based methods.

With regard to RCI methods, change in scores for an individual patient is interpreted in the context of normal healthy variation, such that an observed change in a patient's score needs to fall outside of the standard error of healthy controls' test-retest variability (22). Numerous variations of the RCI have been developed which adjust for factors such as practice effects, and regression to the mean (23). Conversely, regression-based methods employ regression models to predict performance at follow-up from initial test performance. Again, significant differences between a patient's predicted and actual score are used to determine reliable change. The regression-based method additionally allows the inclusion of moderating variables such as age and education, and controls for practice effects and regression to the mean (24). RCI and regression-based methods allow clinicians to interpret patients' change scores or can provide a meaningful interpretation or endpoint for clinical trials.

The aims of this study are: (1) to examine whether practice effects are observed using the ECAS alternate forms over clinically meaningful test-retest intervals; (2) to determine test-retest reliability of the ECAS-A-B-C over clinically meaningful intervals; and (3) to compare common methods for measuring reliable change in a patient's ECAS score across serially administered alternate versions.

Method

Participants

Eighty Irish and Scottish healthy adults were recruited representative of the demographic characteristics of ALS patients. Only those participants who completed the ECAS at two or more timepoints were included in the present study. Fifty-seven participants completed one follow-up assessment, and 51 participants completed two follow-up assessments. Exclusion criteria included: a history of dyslexia or marked premorbid reading or writing difficulties or a learning disability; non-fluent English reading and writing abilities; history of neurological conditions that could affect cognition such as major hemispheric stroke, traumatic brain injury, and severe active epilepsy; alcohol and drug dependencies; and having a known blood relative with ALS. Participants were recruited through a research volunteer panel and through local community noticeboards. Non-blood relatives of ALS patients were also recruited as control participants. All participants provided informed written consent and this research was approved by the University of Edinburgh Psychology Research Ethics Committee and the Beaumont Research Ethics Committee. Participants' travel costs associated with participation were reimbursed.

Procedure

Participants were assessed every four months for three occasions. The ECAS is an ALS-designed measure of cognitive and behavioural functioning. For the purposes of this study, the ECAS behavioural interview was not included. The ECAS consists of three versions (A-B-C) which were designed to be administered serially. Each version of the ECAS consists of 15 parallel tests, categorized into five cognitive domains. Executive, language, and verbal fluency domains are described as ALS Specific functions, while the memory and

visuospatial domains are described as ALS Non-Specific. The ALS-Specific and ALS Non-Specific domains combine to generate a measure of global cognitive functioning, namely, the ECAS Total score. At each assessment point, an alternate version of the ECAS was administered such that the ECAS-A was given at Time 1, the ECAS-B at Time 2, and the ECAS-C at Time 3.

Statistical analysis

Statistical analyses were conducted using R 3.3.2. Change scores were calculated for each time comparison by subtracting the baseline score from the follow-up score, i.e. (Time 2 – Time 1, Time 3 – Time 2, and Time 3 – Time 1). Welch *t*-tests were used to compare change scores between centres to ensure comparability. When data did not meet assumptions of normality, Mann-Whitney *U*-tests were employed. In all cases, Time 1 is synonymous with ECAS-A, Time 2 with ECAS-B, and Time 3 with ECAS-C.

Test-retest reliability: of the alternate forms of the ECAS (A-B-C) was examined using intraclass correlation coefficients (ICC) with mean-rating absolute agreement two-way random effects models. ICC coefficients were calculated for the component (language, fluency, executive, memory, visuospatial) and composite (ALS Specific, ALS Non-Specific, ECAS Total) domains of the ECAS.

Practice effects: were explored using one-way repeated measures analysis of variance models (ANOVA) to examine the presence of a main effect of Time. Repeated measures ANOVAs are limited to balanced designs and only those participants who completed all three time-points were included in this analysis.

Change indices: were calculated using four types of model: two regression-based methods and two reliable change index (RCI) methods. Each method corrects for slightly different moderating effects. The RCI JT method accounts for measurement error, while the Chelune method additionally accounts for practice effects. While significant practice effects in using alternate versions of the ECAS have not previously been found (21), small improvements may be present which might not reach statistical significance. The simple regression method incorporates corrections for regression to the mean, whereby individuals who perform in the extremes tend to converge on the group mean at follow-up. Finally, the multiple regression method allows for the incorporation of potential moderating variables such as age and education that may influence change over time. Given the higher sensitivity of the ALS Specific, ALS Non-Specific, and ECAS Total scores to cognitive impairment against a full neuropsychological battery (13), change score analysis was conducted for these composite domains.

Method 1: RCI (JT method)

The first RCI model calculated was the Jacobson and Truax method (JT method) (25), which accounts for measurement error. The JT method is calculated as the difference between Time 2 and Time 1 divided by the standard error of difference (SE_{diff}) between these two time-points. The standard error of the difference is derived from the standard error of the measurement (SE_m) such that $SE_{diff} = \sqrt{2(SE_m)^2}$. The standard error of the measurement (SE_m) is calculated with the equation $SE_m = s_1\sqrt{1 - r_{xx}}$, where s_1 is the standard deviation of the Time 1 ECAS (i.e. for ECAS-B, the preceding version is ECAS-A, and for ECAS-C the preceding version is ECAS-B) and r_{xx} is the test-retest reliability coefficient between these two ECAS forms. Therefore, the RCI equation using the JT method is calculated with the formula:

$$RCI = \frac{x_2 - x_1}{SE_{diff}}$$

Reliable change is defined by values larger than ±1.645 (two-tailed 90% confidence interval). The formula was then restructured to calculate the upper and lower 'thresholds' of reliable change (X) i.e. the number of points increase/decrease required between two testing sessions, which constitutes a reliable change. Therefore, the equation was restructured as:

$$\pm\Delta X = 1.645(SE_{diff})$$

Method 2: RCI (chelune method)

The second RCI method employed is the Chelune method (26), which corrects for measurement error and practice effects. While the alternate versions of the ECAS were developed to account for practice effects, it is possible that small non-significant improvements continue to exist. Additionally, the accounting for practice effects here may help to account for any small but non-significant differences in difficulty present in the alternate versions. The Chelune method is similar to the JT method, taking the form of:

$$RCI = \frac{(x_2 - x_1) - (\bar{X}_2 - \bar{X}_1)}{SE_{diff}}$$

Here, the denominator is again the standard error of the difference SE_{diff} (i.e. $\sqrt{2(SE_m)^2}$). However, the Chelune method adds a constant as to the numerator to account for systematic changes in performance such as practice effects. This is achieved by calculating the mean difference in performance between Time 2 and Time 1 ($\bar{X}_2 - \bar{X}_1$) and subtracting this from an individual's

change score. As before, this equation was restructured to solve for X resulting in:

$$\Delta X = (\bar{X}_2 - \bar{X}_1) \pm 1.645(SE_{diff})$$

Method 3: Simple linear regression

The first regression-based method employs a simple linear regression model that predicts follow-up performance based on the preceding performance. First, a patient's predicted Time 2 score is calculated using the basic regression equation:

$$\hat{X} = \beta X + C$$

Where $\hat{X}$ is an individual's predicted Time 2 score, β is the beta coefficient for the predictor in the model, X is the Time 1 score, and C is the intercept estimate of the model. Next, the discrepancy between the observed Time 2 score and the predicted Time 2 score is calculated and referred to as the residual (i.e. Time 2 – predicted Time 2). To extract a change index, this residual is then divided by the residual standard error (or standard error of the estimate; *SEE*). When values of the residual divided by the SEE are greater than ±1.645 (two-tailed 90% confidence interval) a reliable change can be determined. To determine reliable change 'thresholds', the equation is restructured to solve for the residual such that:

$$\pm(X - \hat{X}) = 1.645(SEE)$$

Where $(X - \hat{X})$ is the difference between the observed score and the estimated score. The same procedure is used for predicting Time 3 performance from Time 2.

Method 4: Multiple linear regression

The second regression-based method is a multiple linear regression model to explore whether age, education, sex, preceding performance, or testing interval affects the model's prediction. Potential predictors were selected based on their correlation with the respective outcome variable (i.e. ALS Specific, ALS Non-Specific, or ECAS Total scores). A relationship with sex was explored using Mann-Whitney *U*-tests. Variables of interest were entered into each model in a single block and only retained if their individual contribution to the model was significant (i.e. backward elimination). Significantly influential cases were removed based on diagnostic plots. Multiple regression equations, similar to simple linear regression equations, take the form of:

$$\hat{X} = \beta_1 X_1 + \beta_2 X_2 \ldots + \ldots \beta_j X_j + C$$

Where β_1 is the coefficient of the first variable of interest, X_1 is the observed score for the first variable, β_2 is the coefficient for the second variable, and so on to the jth variable. Again, this equation is restructured to solve for $(X - \hat{X})$ such that:

$$\pm(X - \hat{X}) = 1.645(SEE)$$

Results

Fifty-seven participants completed two or more time-points and were included in the present study. Participants were 61.40% male ($n = 35$) with a mean age of 62.32 ± 13.36 years and 14.87 ± 3.19 years of education. Mean test-retest intervals were 4.30 ± 0.66 months and 3.99 ± 0.54 months for T1 to T2, and for T2 to T3, respectively. Mean change scores were calculated for Time 1 to Time 2, Time 2 to Time 3, and Time 1 to Time 3. No significant differences were observed in mean change scores, nor in age, gender, or education between Irish and Scottish participants (all $p > 0.05$) indicating comparability.

Practice effects

Mean test performance for the subdomains of the ECAS and its alternate versions are displayed in Table 1. Mean performance for all cognitive subdomains (language, executive, fluency, memory, and visuospatial) are analogous across time-points, such that no mean difference exceeded 1 point. The resulting ANOVA models produced no significant main effect for executive functions ($F(2,100) = 1.43$, $p = 0.24$), fluency ($F(2,100) = .25$, $p = 0.780$), or memory ($F(2,100) = 1.04$, $p = 0.358$). Additionally, no main effect was observed for the composite ALS Specific ($F(2,100) = .852$, $p = 0.43$), ALS Non-Specific ($F(2,100) = .838$, $p = 0.435$), nor ECAS Total ($F(2,100) = .428$, $p = 0.653$). Due to ceiling

Table 1. Mean scores and standard deviations for the ECAS-A, ECAS-B, and ECAS-C.

	ECAS-A	ECAS-B	ECAS-C
ALS Specific (max 100)	85.65 ± 8.56	86.39 ± 8.55	86.20 ± 9.49
Language (max 28)	27.14 ± 1.87	26.74 ± 2.09	26.76 ± 1.89
Fluency (max 24)	19.61 ± 2.71	19.82 ± 2.43	19.69 ± 4.22
Executive (max 48)	38.89 ± 5.59	39.82 ± 5.37	39.75 ± 5.68
ALS Non-Specific (max 36)	30.14 ± 3.73	29.89 ± 3.66	30.41 ± 3.11
Memory (max 24)	18.46 ± 3.43	18.51 ± 3.13	18.88 ± 2.89
Visuospatial (max 12)	11.68 ± 0.74	11.39 ± 1.00	11.53 ± 0.70
ECAS Total (max 136)	115.79 ± 11.26	116.28 ± 11.38	116.61 ± 11.87

effects and thus the presence of ties in the language and visuospatial subtests, formal analysis was not conducted. However, given the similarity in mean scores and the lack of significant differences for their composite domains, a lack of observable practice effects may be assumed. Therefore, no evidence of practice effects was found for the repeated assessment using the ECAS alternate versions (A-B-C) over clinically relevant test-retest intervals of three to four months.

Test-retest reliability

Two-way absolute agreement mixed effects ICC models were generated for each subdomain of the ECAS (see Supplementary materials). Test-retest reliability was good for the majority of subdomains (i.e. > .70). The only subtest to fall below .70 was the visuospatial domain. However, a lack of variability due to participants reaching ceiling (i.e. over 50% scoring 12 points for each version of the ECAS) will exacerbate small differences in performance rendering this result unreliable (27). With regard to the ALS Specific, ALS Non-Specific, and ECAS Total scores, test-retest reliability was excellent.

Change indices

RCI method: Methods 1 and 2

Reliable change indices (RCI) were calculated for ALS Specific, ALS Non-Specific, and ECAS Total score using the Jacobson and Truax method (JT method) (25) and the Chelune method (26). Thresholds for reliable change are displayed in Table 2, in addition to recommended clinical thresholds. Data used to calculate RCI thresholds are available in Supplementary Table 1. These thresholds provide the number of points increase required to determine a reliable improvement in cognitive performance and the number of points decrease required to determine a reliable decline in functioning. For example, using the JT method, a drop of 8.23 points or greater in ECAS Total score between the ECAS-A and ECAS-B is required for a reliable decline, while an increase of 8.23 points constitutes a reliable improvement. By comparison, using the Chelune method a drop of 7.74 points is required for a reliable decline, or an increase of 8.72 points for a reliable improvement due to the incorporation of practice effects.

Method 3: Simple linear regression

Simple linear regression models were built to predict follow-up scores based on previous performance. Table 3 provides data for calculating predicted ECAS-B performance from ECAS-A, and for predicting ECAS-C from ECAS-B using the equation $\hat{X} = \beta X + C$. This predicted score can then be converted into a change index with ±1.645 constituting a reliable deviation for predicted performance. Alternatively, the column $X - \hat{X}$ in Table 3 provides upper and lower thresholds calculated as $\pm (X - \hat{X}) = 1.645(SEE)$.

Method 4: Multiple linear regression

Variables of interest were explored as potential moderating factors in multiple regression models using correlational analysis. For the ECAS-B, education level significantly correlated with ALS Specific ($r = .42$, $p = 0.002$), ALS Non-Specific ($r = .49$, $p < 0.001$), and ECAS Total ($r = .47$, $p < 0.001$) scores. Age at testing and test-retest interval did not significantly correlate with ECAS-

Table 3. Simple linear regression equations for predicting ECAS-B and ECAS-C performance.

	R^2	*SEE*	C	$\beta_{(ECAS-A)}$	$X - \hat{X}$
Predicting ECAS-B from ECAS-A					
ALS Specific	0.398	5.29	34.18	0.613	±8.70
ALS Non-Specific	0.297	2.25	15.31	0.490	±3.70
ECAS Total	0.448	6.23	41.62	0.648	±10.24
	R^2	*SEE*	C	$\beta_{(ECAS-B)}$	$X - \hat{X}$
Predicting ECAS-C from ECAS-B					
ALS Specific	0.700	5.30	34.18	0.938	±8.72
ALS Non-Specific	0.597	2.00	11.60	0.628	±3.29
ECAS Total	0.741	6.12	14.78	0.872	±10.07

R^2 is the multiple R^2. *SEE* is the residual standard error, C is the intercept, β is the beta coefficient associated with the subscript ECAS, $X - \hat{X}$ is the residual (i.e. the difference between the model predicted score and the observed score). The $X - \hat{X}$ column indicates the number of points difference required between observed and estimated score to determine reliable difference – this is calculated as 1.645*(*SEE*).

Table 2. RCI thresholds for the ECAS-A, ECAS-B, and ECAS-C.

	JT method			Chelune method		
	ALS Specific ΔX	ALS Non-Specific ΔX	ECAS Total ΔX	ALS Specific ΔX	ALS Non-Specific ΔX	ECAS Total ΔX
ECAS-A to ECAS-B	± 7.23	± 3.35	± 8.23	−6.50 < > 7.97	−3.60 < > 3.11	−7.74 < > 8.72
ECAS-B to ECAS-C	± 6.44	± 3.19	±7.18	−6.63 < > 6.25	−2.68 < > 3.70	−6.86 < > 7.51
ECAS-A to ECAS-C	± 6.02	± 2.97	± 6.64	−5.47 < > 6.56	−2.70 < > 3.24	−5.82 < > 7.46
Recommended for clinical use	≥ 8	≥ 4	≥ 9			

ΔX is the change in score required to be considered significant. The Chelune method results in different upper and lower thresholds due to its subtraction of a constant.

Table 4. Multiple regression models to predict ECAS performance.

	R^2	SEE	C	$\beta_{(ECAS\text{-}A)}$	$\beta_{(Education)}$	$X - \hat{X}$	
Predicting ECAS-B from ECAS-A							
ALS Specific	.451	5.01	28.82	.573	.587	± 8.24	
ALS Non-Specific	.297	2.25	15.31	.490	–	± 3.70	
ECAS Total	.483	5.97	37.94	.599	.628	± 9.82	
	R^2	SEE	C	$\beta_{(ECAS\text{-}B)}$	$\beta_{(Education)}$	$X - \hat{X}$	
Predicting ECAS-C from ECAS-B							
ALS Specific	.700	5.30	34.18	.938	–	± 8.72	
ALS Non-Specific	.431	1.87	12.69	.472	.243	± 3.08	
ECAS Total	.741	6.12	14.78	.872	–	± 10.07	
	R^2	SEE	C	$\beta_{(ECAS\text{-}A)}$	$\beta_{(ECAS\text{-}B)}$	$X - \hat{X}$	
Predicting ECAS-C from ECAS-A AND ECAS-B							
ALS Specific	.744	4.81	−1.28	.583	.432	± 7.91	
ALS Non-Specific	.762	1.51	7.37	.473	.289	± 2.48	
ECAS Total	.815	5.11	2.74	.563	.416	± 8.41	
	R^2	SEE	C	$\beta_{(ECAS\text{-}A)}$	$\beta_{(ECAS\text{-}B)}$	$\beta_{(Age)}$	$X - \hat{X}$
ECAS-C performance from ECAS-A, ECAS-B, and age							
ALS Non-Specific	.665	1.42	10.91	.473	.269	−.044	± 2.34

R^2 is the multiple R^2 when model contains one predictor and adjusted R^2 when model contains more than one predictor. *SEE* is the residual standard error, C is the intercept, β is the beta coefficient associated with the subscript, $X - \hat{X}$ is the residual (i.e. the difference between the model predicted score and the observed score). The $X - \hat{X}$ column indicates the number of points difference required between observed and estimated score to determine reliable difference – this is calculated as 1.645*(*SEE*).

B performance, and no significant effect of sex was observed. For the ECAS-C, education level again significantly correlated with ALS Specific ($r = .40$, $p = 0.002$), ALS Non- Specific ($r = .31$, $p = 0.02$), and ECAS Total ($r = .40$, $p = 0.002$) scores. The ALS Non-Specific functions of ECAS-C significantly correlated with age ($r = -.32$, $p = 0.02$) and test-retest interval ($r = -.30$, $p = 0.03$). Additionally, a marginally significant Mann-Whitney *U*-test was observed for sex and ALS Specific functions of ECAS-C ($W = 207$, $p = 0.047$). While these variables are retained for the regression models, the significant correlations with age, sex, and test-retest interval do not survive Holm correction for multiple comparisons (all $p > 0.05$).

Significant variables were entered into regression models in a single block and individual variables were only retained once their contribution to the model remained significant. For the multiple regression models, the variance inflation factor for the predictors did not exceed 2. Table 4 displays the results of these models. For the prediction of ECAS-B, education is retained in the model for ALS Specific and ECAS Total scores. For the ECAS-C, education significantly added to the model for ALS Non-Specific scores. No other variables were retained in the final multiple regression models. Additional models were generated to predict ECAS-C from the combined performance on ECAS-A and ECAS-B. As with the previous multiple regression models, variables of interest were correlated with, and regressed onto, the ECAS-C. However, in this instance, the only variable retained is that of age on ALS Non-Specific.

Example data

A 62-years-old male limb-onset ALS patient with 10.5 years of education was assessed at two time-points, with a four-month interval between Time 1 and Time 2. The patient had no behavioural or respiratory symptoms at either time-point. For the ECAS total, the patient scored 108 on the ECAS-A, and 96 on the ECAS-B. This resulted in change scores of −12 which falls below the RCI threshold for significant decline by both the JT method and the Chelune method, and the recommended clinical thresholds (Table 2).

Using the simple regression-based method, this patient's predicted ECAS-B score is calculated using the equation $\hat{X} = \beta X + C$, where in this case $\hat{X} = (.648)(108) + 41.62$. The resulting predicted ECAS-B score is therefore 111.60 with a residual (i.e. ECAS-B minus predicted ECAS-B) of −15.2. These values are the entered into the equation $\frac{(X-\hat{X})}{SEE} = \frac{(96-111.60)}{6.23} = -2.44$ which is less than −1.645). Therefore the patient's score was significantly lower than predicted. Furthermore, the residual of −15.2 falls below the simple regression-based threshold of ±10.24. The multiple regression-based method includes the variable education, here 10.5 years, with the equation

$\hat{X} = \beta_A X_A + \beta_{Ed} X_{Ed} + C$. The patient's predicted score is then $\hat{X} = (.599)(108) + (.628)(10.5) + 37.94$ which results in a predicted ECAS-B score of 109.23. Using the same equation as above, $\frac{(X-\hat{X})}{SEE} = \frac{(96-109.23)}{5.97} = -2.22$. Again, this falls outside of ± 1.645, and the residual (-13.23) is less than the threshold of ± 9.82. Therefore, under all measures, the patient presents with a significant and reliable decrease in cognitive functioning.

Discussion

The monitoring of cognitive and behavioural symptoms longitudinally in ALS is integral to measurement of progression of disease, outcome of clinical trials and in providing person-centred care. While the recent development of alternate forms of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) provided tools necessary to assess neuropsychological functioning over time, the present paper aimed to provide data necessary for individual-level interpretation. Moreover, thresholds for significant decline or improvement provide viable end-points for clinical trials. An additional goal was to explore the test-retest reliability of the ECAS's alternate forms when testing across clinically relevant intervals. The present results demonstrate that the alternate versions of the ECAS provide a consistent method by which cognitive functioning can be monitored over time in patients with ALS. Building from the study by Crockford et al. (21), the present study aimed to explore whether the alternate forms of the ECAS ameliorate practice effects when administered over clinically-meaningful testing intervals. No significant practice effects were observed for the ECAS-A, ECAS-B, and ECAS-C when administered sequentially. The alternate forms of the ECAS are successful in ameliorating practice, thus confirming the findings of the authors (21).

The test-retest reliability of the alternate forms was additionally explored. Intraclass correlation coefficients (ICCs) were excellent for the composite ALS Specific, ALS Non-Specific, and ECAS Total scores. The individual cognitive subtests of ECAS performed well also, achieving ICC values greater than .70. While the ICC values for the visuospatial task appear quite low, this is in part due to the dependency of the ICC calculation on between-subjects variability. Because there is very little between-subject variability in the visuospatial task, the small differences present are exaggerated suggesting a smaller test-retest reliability than is warranted (27). However, as noted, the composite ALS Specific, ALS Non-Specific, and ECAS Total reliability was excellent. This is particularly pertinent given the sensitivity of these domains in detecting cognitive impairment against a full neuropsychological battery (13). As such, participants who were administered the ECAS forms serially showed good consistency and stability across testing sessions.

The primary aim of this paper was to establish methods of interpreting reliable change for patients with ALS. Four models were utilized, including two reliable change indices (RCI) and two regression based (RB) methods. These methods account for slightly different factors that may influence performance change. The RCI thresholds for reliable change are the minimum increase or decrease in performance necessary to be considered reliable. Both RCI methods produced similar thresholds for all comparisons (i.e. ECAS-A to ECAS-B, ECAS-B to ECAS-C, and ECAS-A to ECAS-C).

The RCI methods proposed by Jacobson and Truax (25) and modified by Chelune et al. (26) were developed on the assumption of repeated assessment using the same version of a test. For instance, the SE_m in these authors' studies is calculated using the standard deviation and test-retest reliability of the same instrument. This does not pose an issue when one considers that the test-retest reliability used in the present study is the intraclass correlations between two ECAS forms. However, RCI calculations traditionally use the standard deviation of the instrument assuming equality of variation for Time 1 and Time 2. Fortunately, the standard deviations for ALS Specific, ALS Non-Specific, and ECAS total across alternate forms were only trivially different (e.g. for ECAS Total scores, the standard deviations were 11.26, 11.38, and 11.87 for the ECAS-A, ECAS-B, and ECAS-C, respectively). It was not deemed necessary to use a measure of shared variance in place of standard deviation.

With regard to the regression-based methods, linear regression models provide predictive scores for patients based on their baseline ECAS performance, or a combination of this and demographic variables. The deviation from a patient's predicted score and their actual score is used to determine whether a deviation constitutes a reliable difference. By dividing the residual by the standard error of the residual, one can determine if an individual's departure from their predicted performance is within normal variation, i.e. variation due to measurement error, practice effects, or regression to the mean. While regression-based methods may be more complicated to calculate, they may also provide more accurate predictions that take account of important moderating variables such as education level. However, some authors have argued that regression-based methods are not necessarily superior to RCI methods (e.g. (19)). Additionally, regression-based methods do have their own limitations. As noted by Crawford and Garthwaite (24), the error associated with predicting follow-up performance from baseline performance using regression based techniques will be larger at the extremes, i.e. the residuals at the extremes are greater. Therefore, caution should be paid to interpreting

change of patients who score poorly at baseline. Because the sample herein is of healthy controls while the target patient population would be expected to score toward the lower extremes, further research would be needed to clarify whether RCI and regression-based thresholds need to be developed based on initial test performance. This may be achieved by exploring these thresholds in a sample of MND patients where cognitive deterioration is not expected or found, for example in patients who possess a slower disease progression.

An important caveat in utilizing these thresholds is that the ECAS is a cognitive screening tool, and not designed to replace full neuropsychological assessment. While a patient's test-retest performance may be reliably described as a decline using the thresholds herein, such findings should be corroborated with specialist neuropsychological input.

In deciding which method to utilize for detecting reliable change, a pragmatic approach is recommended. For research purposes, the multiple regression-based methods may provide more specific indicators of change. However, these regression-based methods are relatively more technical and complex to calculate. The ECAS was designed to be accessible to non-specialist health care professionals, and thus, the recommendation of regression-based methods may compromise the clinical utility of the ECAS. Given the similarity in scores across all four methods and the ease with which RCI methods can be included in a clinical environment, a conservative application of change scores is recommended for clinical purposes. Based on the most conservative JT method, and to reduce the number of false-positives, a change of $\geq$8, $\geq$4, or $\geq$9 points is recommended for a significant change in ALS Specific, ALS Non-Specific, or ECAS Total score, respectively.

Conclusions

Measuring the progression of cognitive symptoms in ALS has important clinical implications. Cognitive status can play an important role in how patients engage with interventions, in how clinicians engage with patients, and in what services may be appropriate. The alternate forms of the ECAS provide a method by which cognitive symptoms can be monitored over time. The present study built on this by providing a means by which a patient's change over time can be reliably interpreted. Four models of change indices were calculated. The reliable change indices may be the method with the highest clinical utility; however, regression based methods may play a role in more detailed analysis or clinical research. Additionally, the present study demonstrated that the test-retest reliability of the ECAS and its alternate forms is excellent for the ALS Specific, ALS Non-Specific, and ECAS Total scores. This, along with no evidence of significant practice effects, suggests that the ECAS-A-B-C are stable, consistent, and useful in monitoring ALS patients' cognitive performance over time.

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Declaration of interest

Orla Hardiman has received fees for consultation work from Biogen Idec, Cytokinetics and Novartis. She serves as Editor-in-Chief of Amyotrophic Lateral Sclerosis. Ammar Al-Chalabi has consulted for Biogen Idec, Cytokinetics Inc, OrionPharma, Mistubishi-Tanabe Pharma and Chronos Therapeutics.

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Supplementary material available online

In Chapter 3, it was demonstrated that the ECAS-A-B-C possess no significant practice effects and high test-retest reliability over clinically meaningful time periods. Metrics of reliable change were provided using four approaches with clinically recommended cut-offs. The evidence provided in Chapters 2 and 3 provide strong evidence for the equivalence and utility of the ECAS alternate forms in the longitudinal monitoring of cognition in ALS. As such, Chapters 2 and 3 were successful in meeting Aim 1; namely, to develop, and validate, alternate forms of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) to accommodate repeated longitudinal assessment in ALS. These findings provide the foundation for the use of the ECAS alternate forms within the clinic.

Thus, it is now possible to explore the evolution of neuropsychology health over the course of ALS while overcoming limitations imposed by the disease (e.g., motor weakness) and assessment (i.e., practice effects).

CHAPTER 4: ALS specific cognitive and behavioural changes associated with advancing disease stage in ALS

In Chapters 2 and 3, a means of observing cognitive functioning over time was demonstrated using the ECAS-A-B-C. This, taken with the King's Clinical Disease Staging provide the opportunity to explore how cognition and behaviour evolves over the course of the disease. The King's Clinical Disease Staging system provides a standardised metric of disease progress, which is superior to time or the functional rating scales (see Chapter 1 for discussion). As such, Chapter 4 explores how the ECAS relates to clinical disease stage cross-sectionally.

Cross-sectionally, a cohort of ALS patients were recruited from three research sites: Edinburgh, Dublin, and London. Assessment of cognition and behaviour were conducted using the original ECAS form and compared against each patients' disease stage using the King's Clinical Staging System. This study allows for the examination of whether a patients' neuropsychological functioning is related to disease stage. Specifically, this chapter will examine whether neuropsychological symptoms are more severe or widespread in advanced disease stages.

The following chapter was accepted for publication by open access (CC-BY) in Neurology. Supplementary materials published with this article are available in Appendix IV.

Title: ALS Specific cognitive and behaviour changes associated with advancing disease stage in ALS.

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Supplementary materials: comparison of patient and control cognition; correlations between cognition, behaviour and disease variables; and cognitive performance for patients with and without bulbar involvement.

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4.1. Abstract

Objective: The purpose of this study is to elucidate the relationship between disease stage in ALS, as measured using the King's Clinical Staging System, and cognitive and behavioural change using the Edinburgh Cognitive and Behavioural ALS Screen (ECAS).

Methods: A large multicentre observational cohort of 161 cross-sectional patients with ALS and 80 healthy matched controls were recruited across three research sites (Dublin, Edinburgh, London). Participants were administered the ECAS and categorised into independent groups based on their King's Clinical Disease Stage at time of testing.

Results: Significant differences were observed between patients and controls on all subtests of the ECAS, except for visuospatial functioning. A significant cross-sectional effect was observed across disease stages for ALS Specific functions (executive, language, letter fluency), and ECAS total score, but not for ALS Non-Specific functions (memory, visuospatial). Rates of ALS-Specific impairment and behavioural change also related to disease stage. The relationship between cognitive function and disease stage may be due to letter fluency impairment, whereas higher rates of all behavioural domains were seen in later King's stage. The presence of bulbar signs, but not site of onset, significantly related to ALS Specific, ECAS Total, and behavioural scores.

Conclusions: ALS specific cognitive deficits and behavioural impairment are more frequent with more severe disease stage. By end-stage disease only a small percentage of patients are free of neuropsychological impairment. The presence of bulbar symptoms exaggerates the differences observed between disease stages. These findings suggest that cognitive and behavioural change should be

incorporated into ALS diagnostic criteria, and should be included in future staging systems.

4.2. Introduction

Amyotrophic Lateral Sclerosis (ALS) is marked by progressive degeneration of motor neurons, with death usually occurring 2-3 years from onset (Al-Chalabi & Hardiman, 2013). Approximately 35% of ALS patients experience cognitive or behavioural impairment, with an additional 15% having frontotemporal dementia (FTD) (Goldstein & Abrahams, 2013; Phukan et al., 2012).

Executive dysfunction is commonly reported in ALS in addition to impairment in language and social cognition (Abrahams et al., 2000; Abrahams et al., 2004; Phukan et al., 2012; Taylor et al., 2013; Van der Hulst, Bak, & Abrahams et al., 2015), whereas apathy is the most frequently reported behavioural feature (Radakovic et al., 2016, Grossman et al., 2007). Longitudinal studies of cognition in ALS have been confounded by small numbers, the use of clinic based populations, and attrition (Abrahams, Leigh, & Goldstein, 2005a; Schreiber et al., 2005; Gordon et al., 2010). However, existing data (Elamin et al., 2013) indicates that cognitive change may relate to indirect measures of disease progression (for example, total score on the ALS Functional Rating Scale-Revised (ALSFRS-R), suggesting that this third domain should be included in diagnostic criteria and staging systems, such as the King's Clinical Staging System (Roche et al., 2012).

The objective of this study was to examine the clinical presentation of cognitive and behavioural symptoms across different disease stages of ALS as

defined by the King's Clinical Staging System. Specifically, the aim was to examine a) whether cognition and behaviour is related to advancing disease stage in a clinically representative sample of ALS patients, b) which domains of cognition and behaviour are particularly related to disease stage, and c) which, if any, clinical variables relate to cognition and behaviour in ALS.

4.3. Materials and Methods

4.3.1. Standard Protocol Approvals, Registrations, and Patient Consents

This study is a multicentre cross-sectional observational study. All participants provided informed written consent and this research was approved by the South-East Scotland Research Ethics Committee, and the Medical Research Ethics Committee of Beaumont Hospital, Dublin.

4.3.2. Participants

One hundred sixty-one patients meeting revised El Escorial diagnostic criteria for possible, probable, or definite ALS (Brooks et al., 2000) were included. Patients were prospectively recruited across three research centres in Edinburgh, Dublin, and London between July 2014 and July 2016. Of the patients recruited, 88.8% were incident cases (n = 143) being assessed within 12 months of diagnosis. Recruitment was population-based in Dublin, and through ALS clinics in Edinburgh and London. Exclusion criteria included: a history of dyslexia, marked premorbid reading or writing difficulties, or a learning disability; non-fluent premorbid English reading and writing abilities; history of other neurological conditions that could affect cognition such as major hemispheric stroke, traumatic

brain injury, and severe active epilepsy; alcohol and drug dependencies; and severe physical disability or weakness at time of assessment prohibiting participation. Of the 161 participants with ALS, 149 primary caregivers consented to provide behavioural data. Eighty demographically matched healthy adults were additionally recruited as a control group. Healthy controls met the same inclusion criteria as the patient group and were not a blood relative of a person with ALS. The control group were recruited through research volunteer panels held by the University of Edinburgh and Trinity College Dublin, non-blood relatives of ALS patients, and local community noticeboards.

4.3.3. Procedure and Materials

Clinic- and home-based semi-structured interviews were conducted to collect demographic and clinical data. Socioeconomic Status (SES) was measured using the National Statistics Socio-Economic Classification (NS-SEC) Self-Coded Scale (Standard Occupational Classification, 2010) modified to include the category of long-term unemployed. Functional status was assessed using the revised ALS Functional Rating Scale (ALSFRS-R) (Cedarbaum et al., 1999). Mood was measured using a modified version of the Hospital Anxiety and Depression Scale (HADS), which excludes items confounded by motor disability (Abrahams et al., 1997; Gibbons et al., 2011).

Clinical staging was measured using the King's Clinical Staging System (Roche et al., 2012, Fang et al., 2017). Each stage of the disease is based on regions of involvement where regions are bulbar, upper limbs, lower limbs, and respiratory or nutritional domains. Stage 1 is defined as the involvement of one bodily region (e.g., an upper limb); Stage 2 is defined as the involvement of two

bodily regions (e.g., upper limb and lower limb); Stage 3 is defined as involvement of three bodily regions (i.e., upper limb, lower limb, and bulbar); and Stage 4 is defined as respiratory or nutritional insufficiency requiring intervention. Regional involvement was determined by the presence of functional signs (e.g., changes in speech) or clinical examination (e.g., fasciculations, wasting of first dorsal interosseous). Respiratory and nutritional insufficiency was determined as per the NICE guidelines for Motor Neuron Disease Assessment and Management (NICE, 2016), including arterialised capillary blood gas tensions, nocturnal arterial oxygen saturation, forced vital capacity, or sniff nasal inspiratory pressure. The King's system has demonstrated good prognostic utility, providing a linear and standardised metric of disease progression (Roche et al., 2012; Fang et al., 2017; Balendra et al., 2015)

Neuropsychological status was measured using the Edinburgh Cognitive and Behavioural ALS Screen (ECAS)(Abrahams et al., 2014). The ECAS is independent of motor disability and consists of 16 subtests across five cognitive domains: language functions, executive functions, and letter fluency combine to generate a composite ALS Specific score, while memory and visuospatial functioning combine to form an ALS Non-Specific score. The ECAS also consists of a carer behavioural interview based on the Rascovsky criteria for behavioural variant Frontotemporal Dementia (Rascovsky et al., 2011). The behaviour interview is a structured clinical interview conducted in private with patients' caregivers. The interview measures five domains of behaviour: behavioural disinhibition; loss of sympathy/empathy; apathy or inertia; perseverative, stereotyped, or compulsive/ritualistic behaviours; or hyperorality and dietary changes. The behaviour interview additionally includes three questions

measuring the presence of psychotic features. Behavioural data gathered at the Dublin site, and the presence/absence of behaviour features was supported by the Beaumont Behaviour Inventory (Elamin et al., 2017). The ECAS was selected as the primary outcome measure to reduce the burden of participation due to its brevity and independence on motor speed, thereby reducing bias in participation.

4.3.4. Statistical Analyses

Demographic, clinical, and neuropsychological data for the patient and control groups were compared using a χ^2 test for categorical data (or Fisher's exact test when expected cell frequencies fell below 5) or Welch t-tests and one-way analyses of variance for continuous data. Effect sizes for group comparisons were calculated using η^2, Cramer's V, and *r* for Mann Whitney U tests. The relationship among ECAS subdomains were explored using tetrachoric correlation analysis. To examine whether cognition or behaviour is related to disease stage, patients with ALS were divided into independent groups based on their King's clinical disease stage at time of testing. Jonckheere-Terpstra Tests were employed on raw ECAS scores specifying a decreasing trend for cognition and an increasing trend for behaviour with *p*-values approximated under the central limit theorem for 10,000 permutations. The ALS Specific, ALS Non-Specific, and ECAS Total scores were the primary cognitive outcome measures due to their high sensitivity to cognitive impairment against a full neuropsychological battery (Niven et al., 2015, Pinto-Grau et al., 2017). The number of reported behaviour domains (max 5) of the ECAS behaviour interview was the primary behavioural outcome measure. When significant relationships were observed, the respective ALS Specific (Language, Executive, and Fluency),

ALS Non-Specific (memory and visuospatial), and behaviour (apathy, disinhibition, loss of sympathy/empathy, perseverative, and eating behaviours) subdomains were analysed to explore the nature of this relationship.

Cognitive impairment was determined using local validated abnormality cut-off scores from UK and Irish populations (Niven et al., 2015, Pinto-Grau et al., 2017). Behavioural impairment was defined as the presence of two or more behavioural features or the presence of apathy, as described by the recent consensus guidelines for diagnosing frontotemporal spectrum disorder (Strong et al., 2017). Rates of impairment between disease stages was analysed with the Cochran-Armitage Test, which evaluates the significance of an increasing binomial proportions trend across an ordinal grouping variable.

The relationship between neuropsychological performance and clinical variables was also explored using one-way analyses of variance (ANOVA), Wilcoxon Mann-Whitney, and Spearman correlation tests. For all analyses, when data violated statistical assumptions, log or power transformation were applied. When transformation failed to correct violations, non-parametric alternatives were used. Multiple comparisons were corrected for using the Holm-Bonferroni method. Missing values were excluded pairwise, unless otherwise stated. Analyses were conducted using R 3.3.2 with alpha set to .05.

Data availability

Anonymised data presented in this article will be made available at the request of a qualified investigator. Requests should be made to Sharon Abrahams (s.abrahams@ed.ac.uk). Supplemental data available from Dyrad.

4.4. Results

ALS patients and control demographic data are presented in Table 4.1. No significant differences were observed between the patient and control group for background variables or levels of depression and anxiety. 64% (*n* = 103) of patients had classical ALS, with symptom onset in the upper or lower limbs, 26% *(n* = 41) had bulbar onset, 9% (*n* = 15) had mixed onset, and 1% (*n* = 2) had respiratory onset.

ALS patients' cognitive performance was compared to that of the control group for each domain of the ECAS. Significant differences were observed for language, executive functions, letter fluency, and memory, while no significant difference was observed for visuospatial functioning. The composite ALS Specific, ALS Non-Specific and ECAS total score all demonstrated significant between-group differences (see supplementary tables). 28.5% of patients were found to have cognitive impairment on the ECAS Total, 27% on ALS Specific, and 19.4% on ALS Non-Specific Scores. Letter fluency impairment was most commonly observed (30.4%), followed by executive (22.5%) and language (21.3%) dysfunction. Memory (16.8%) and visuospatial (9.4%) impairment were less commonly found.

Of the 149 patients for whom behavioural data were available, 45% had no behavioural features, 21.5% with one feature, 14.1% with two features, and

Table 4.1. Demographic data for patients with ALS and control participants (ALS = 161; Controls = 80)

	ALS	Control	*t* or *W* or χ^2	*P*-value
Dublin *n*	86	43		
Edinburgh *n*	53	37		
London *n*	22	-		
Sex (% male)[a]	67.1	60	0.884	0.347
Education (years)	13.93 ± 3.52	14.49 ± 3.31	1.22	0.224
Age at testing (years)	61.39 ± 11.58	60.83 ± 13.23	0.326	0.745
SES (median)[a]	2 ± 1.48	2 ± 1.48	6874.5	0.090
HADS anxiety[a]	4 ± 2.97	3.5 ± 2.22	6064	0.588
HADS depression[a]	1 ± 1.48	1 ± 1.48	6682	0.057
Age at onset (years)	59.42 ± 11.75			
Diagnostic delay (months; median)	12 ± 8.9			
Riluzole use (% yes)	75.8			
Site of onset (B/U/L/R/M; %)	26/29/35/1/9			
Months since diagnosis (median)	3 ± 2.97			
ALSFRS-R	38.28 ± 6.94			
King's Clinical Stage (Stages 1/2/3/4; %)	25/28/14/34			

Note. Values are mean ± one standard deviation. [a]Wilcoxon-Mann-Whitney test. For these and Diagnostic delay, values are median ± median absolute deviation. SES = Socioeconomic status; HADS = Hospital Anxiety and Depression Scale; Site of onset: B=Bulbar, U=Upper limb, L=Lower limb, R=respiratory, M = Mixed onset. Diagnostic delay is the time from symptom onset to diagnosis. ASLFRS-R = ALS Functional Rating Scale – Revised. Mood data was unavailable for 12 patients and two controls. SES unavailable for 7 patients and 1 control.

19.5% with three or more features. Behavioural impairment as described by the revised consensus guidelines (Strong et al., 2017) was found in 39.6% of patients. Apathy was the most commonly reported behavioural feature (30.9%), followed by a loss of sympathy/empathy (27.5%), changes in eating behaviours (24.8%), perseveration (24.8%), and disinhibition (15.4%).

Impairment in cognitive domains was most strongly associated with other cognitive domains, rather than behavioural features, and vice versa (see supplementary see supplementary tables and figures). Language, fluency, executive, and memory impairment co-occurred (r_{tet} = .27 - .49). Similarly, the co-occurrence of behavioural features was strong ranging from .37 - .79. The

relationship between cognition and behaviour was weaker, with a few exceptions. Relationships were observed between sympathy/empathy and executive dysfunction (r_{tet} = .37), disinhibition and fluency impairment (r_{tet} = .38), and visuospatial impairment with perseveration (r_{tet} = .44) and hyperorality (r_{tet} = .35).

4.4.1 Cognition, Behaviour, and King's Clinical Disease Staging

Patients were divided into their respective King's Clinical Stage at time of testing. Demographic and clinical variables are described for each disease stage group in Table 4.2. No significant differences were observed between the four patient groups for most variables. As expected, ALSFRS-R scores significantly differed between disease stages ($F(3, 146) = 25.97$, $p < .0001$, $\eta^2 = .348$). A significant dependency was observed between site of onset and disease stage ($\chi^2(6) = 17.38$, $p = .008$, $V = .247$) driven by a higher proportion of bulbar onset patients, compared to upper-limb onset, in Stages 1 and 4 (standardised residuals of 1.44 and 1.42), and the inverse for Stages 2 and 3 (residuals of -1.80 and -1.48 respectively). Differing levels of depressive symptoms as measured by the HADS were observed across disease stages ($H(3) = 18.18$, $p < .001$). Post-hoc analysis showed that Stage 1 significantly differed from Stage 2 ($p = .043$, $r = .262$) and Stage 4 ($p < .001$, $r = .430$).

Table 4.2. Demographic and clinical variables by King's Clinical Disease Stage

	Stage 1[a] *n* = 40	Stage 2[a] *n* = 45	Stage 3[a] *n* = 22	Stage 4[a] *n* = 54	*F* or χ^2	*P*-value
Demographic Variables						
Age at testing	62.15 ± 10.59	60.07 ± 12.25	59.68 ± 12.63	62.63 ± 11.39	0.578	0.630
Sex (% male)	72.5	66.7	77.2	59.3	3.07	0.382
Education (years)	13.88 ± 4.07	14.10 ± 2.99	15.21 ± 4.16	13.31 ± 3.16	1.44	0.233

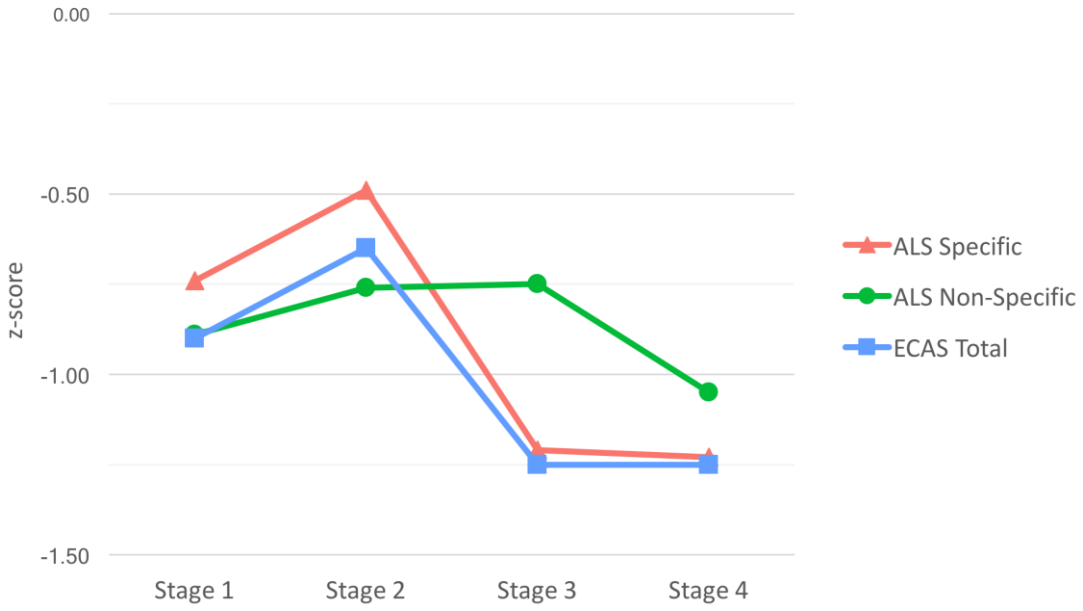
SES [b]	2.5 ± 2.22	2.0 ± 1.48	2.0 ± 1.48	2.0 ± 1.48	1.05	0.788
Clinical Variables						
Age at onset	60.27 ± 10.78	58.22 ± 11.97	57.59 ± 13.27	60.59 ± 11.80	0.576	0.632
Diagnostic delay (months) [b]	10.5 ± 9.64	12.0 ± 7.41	9.50 ± 8.15	11.0 ± 7.41	0.180	0.910
Site of onset: B/U/L/R/M (%)	41/23/35/0/0	13/47/36/0/4	9/36/41/0/14	34/18/24/4/20	17.38	0.008
Regions involved (% yes):						
Bulbar	37.5	32.4	100.0	64.8	-	-
Upper limb	22.5	86.7	100.0	85.2	-	-
Lower limb	40.0	88.9	100.0	72.2	-	-
Respiration	0	0	0	85.2		
Riluzole use (% yes)	80.0	75.6	77.3	72.2	0.788	0.852
Time since onset (months)[b]	15.0 ± 9.3648	14.0 ± 10.38	15.0 ± 13.34	17.0 ± 8.90	0.196	0.899
Time since diagnosis (months) [b]	3.0 ± 2.97	2.0 ± 2.97	2.50 ± 2.22	3.0 ± 2.97	1.937	0.712
ALSFRS-R	43.49 ± 2.94	39.48 ± 4.81	38.10 ± 5.24	33.59 ± 8.01	25.97	< 0.0001
HADS Anxiety [b]	3.0 ± 1.48	4.0 ± 2.97	4.0 ± 3.71	5.0 ± 3.71	2.99	0.393
HADS Depression [b]	0.0 ± 0.0	2.0 ± 2.97	2.0 ± 2.97	3.0 ± 2.97	18.18	< 0.001
Anxiety Case level (%)[c]	5.4	4.8	10	18	-	.149
Depression Case level (%)[c]	0	4.8	10	14	-	.053

Note. [a] Unless otherwise stated, values are mean ± one standard deviation. [b] Values are median ± median absolute deviation. [c] Fisher Exact Test; Case level of anxiety ≥ 9; case level of depression ≥ 8. SES = Socioeconomic status; ALSFRS-R = ALS Functional Rating Scale Revised. HADS = Hospital Anxiety and Depression Scale; Site of onset: B=Bulbar, U=Upper limb, L=Lower limb, R= Respiratory, M = Mixed onset, for statistical analysis, respiratory onset patients dropped.

Cognitive performance (represented as a z score calculated against local normative data) for patients within each disease stage is presented in Figure 4.1, with raw scores presented in Table 4.3. To explore whether cognitive and behavioural performance differs between disease stages, Jonckheere Terpstra Tests were employed on ECAS raw scores. A significant effect, corrected for multiple comparisons, was observed for ALS Specific (T_{JT} = 3804.5, p = .022), ECAS Total (T_{JT} = 3845.5, p = .026), and the number of behavioural features (T_{JT} = 5295.5, p < .001) demonstrating lower cognitive ability and a higher number of behaviour features across advancing disease stages. No significant effect was observed for ALS Non-Specific functions. To examine which domains of ALS

Specific functions were driving this result, analysis of the ALS Specific and behavioural subdomains was conducted.

Figure 4.1. Cognitive performance across King's Clinical Disease Stages



Note. Patient performance is scaled to a standardised score (z-score) based on the mean and standard deviation of local UK and Irish control groups.

Executive functions (T_{JT} = 4061, p = .035) and letter fluency (T_{JT} = 3721.5, p = .001) scores significantly related to more advanced disease stages; however, after correcting for multiple comparisons, only letter fluency remained significant (p = .002). Analysis of the behavioural domains showed that apathy (z = 4.00, p < .001), disinhibition (z = 2.65, p = .012), loss of sympathy or empathy (z = 3.06, p = .005), perseveration (z = 1.679, p = .036), eating behaviours (z = 2.76, p = .012) significantly related disease stages after correcting for multiple comparisons (see Figure 4.2). The presence of psychotic features was also more common in later disease stages (z = 2.45, p = .014). Thus, cognitive functions

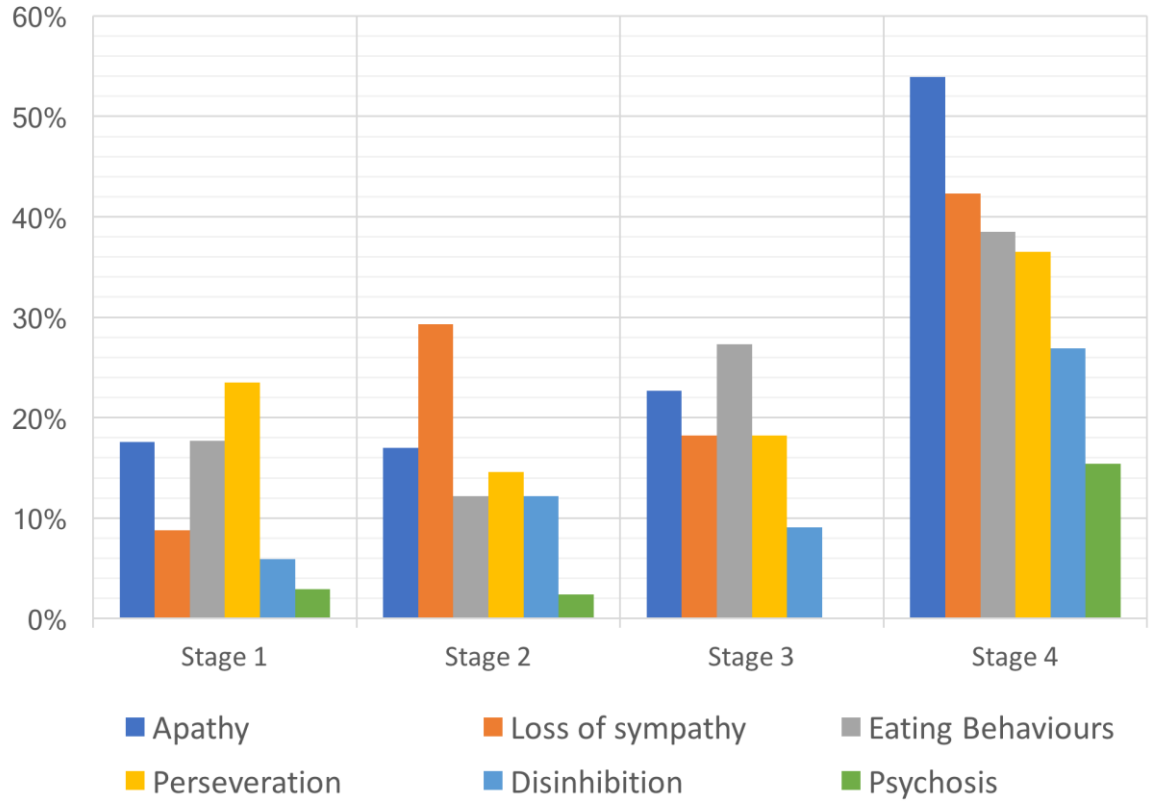
specific to ALS (particularly letter fluency), behaviour (apathy, disinhibition, loss of sympathy/empathy, perseveration, and disinhibition), and psychosis are significantly associated with disease stage with later stages relating to more severe neuropsychological symptoms. These findings are consistent when the sample is restricted to incident cases only.

Table 4.3. Cognitive and behavioural data across King's Clinical Disease Stage

	Control[a] *n* = 80	Stage 1[a] *n* = 39	Stage 2[a] *n* = 45	Stage 3[a] *n* = 22	Stage 4[a] *n* = 55
Cognitive Domains					
ALS Specific (0-100)	84.26 ± 9.12	78.15 ± 13.32	80.76 ± 9.77	74.76 ± 15.12	73.06 ± 14.67
Language[b] (0-28)	28.0 ± 0.0	27.0 ± 1.48	27.0 ± 1.48	27.0 ± 1.48	27.0 ± 1.48
Executive (0-48)	38.27 ± 5.89	35.00 ± 7.55	36.76 ± 6.24	32.86 ± 8.90	32.72 ± 8.46
Fluency (0-24)	19.07 ± 2.95	17.20 ± 4.29	17.87 ± 3.87	15.64 ± 5.51	14.67 ± 5.71
ALS Non-Specific (0-36)	29.98 ± 3.76	27.00 ± 6.07	28.00 ± 3.97	27.73 ± 4.41	25.98 ± 6.21
Memory (0-24)	18.27 ± 3.43	15.88 ± 4.97	16.20 ± 3.93	16.14 ± 4.17	14.31 ± 5.81
Visuospatial[b] (0-12)	12.0 ± 0.0	12.0 ± 0.0	12.0 ± 0.0	12.0 ± 0.0	12.0 ± 0.0
ECAS Total (0-136)	114.24 ± 11.65	105.08 ± 18.01	108.76 ± 12.08	102.24 ± 18.47	100.08 ± 17.37
Behaviour					
ECAS Behaviour[b] (0-5)	-	0.0 ± 0.0	0.0 ± 0.0	1.0 ± 1.48	2.0 ± 1.48
Psychosis (% yes)	-	2.9	2.4	0.0	15.4

Note. [a]Values are mean ± one standard deviation unless otherwise stated. [b]Median ± median absolute deviation are reported.The language, executive, and visuospatial domains of the ECAS were each missing one data point. Behaviour is the number of behavioural dimensions (max 5). Psychosis is defined as the presence one of more of the three measured features. Score ranges for each cognitive and behavioural domain are presented in parentheses.

Figure 4.2. Frequency of behavioural impairment across King's Clinical Disease Stages



While Stage 4 is a marker of end-stage disease, it may be considered a prognostic indicator rather than indicating more severe spread of pathology. As such, data were re-analysed excluding Stage 4 patients without bulbar, upper limb, and lower limb involvement (n = 130), with the majority of results unchanged. The significant effect for ECAS Total (T_{JT} = 2514, p = .039), ALS Specific functions (T_{JT} = 2477.5, p = .017), and behaviour persisted (T_{JT} = 3438, p < .001), with behaviour surviving correction for multiple comparisons (p < .001). Examination of the ALS Specific domains reveal that letter fluency is significant after correction (T_{JT} = 2483, p = .020). Cochran-Armitage tests of behaviour domains reveal that apathy (z = 2.85, p = .009), disinhibition (z = 3.73, p < .001),

loss of sympathy or empathy (z = 3.15, p = .004), eating behaviours (z = 2.51, p = .018) and psychosis (z = 2.07, p = .039) remained significant. Re-analysis of data with Stage 4 removed entirely reveals no significant effect for disease stage.

4.4.2. Rates of Neuropsychological Impairment and King's Clinical Disease Stage

Consistent with the analyses of the raw scores, a significant effect for higher rates of impairment was observed across disease stages for ALS Specific after correcting for multiple comparisons (See Table 4.4). Of the ALS Specific subdomains, a significant relationship was observed (z = 3.54, p < .001) for letter fluency impairment (see Figure 4.3). While rates of impairment for ALS Non-Specific functions differed between Stages 3 and 4, this did not reach statistical significance. Rates of behavioural impairment were significantly higher in more advanced disease stages.

Patients were classified as neuropsychologically intact if there was no evidence of behavioural impairment and no evidence of cognitive impairment (ALS Specific, ALS Non-Specific, ECAS Total). Patients for whom behavioural data were unavailable were not included in this classification. A significant effect was found for lower rates of neuropsychologically intact patients, such that by Stage 4, only 19.6% of patients were free of impairment. The effect of disease stage on rates of impairment did not change when data were restricted to incident cases. No change in results was observed when Stage 4 patients without concurrent involvement of bulbar, upper limb, and lower limb regions were removed. Results did not survive the removal of Stage 4 patients.

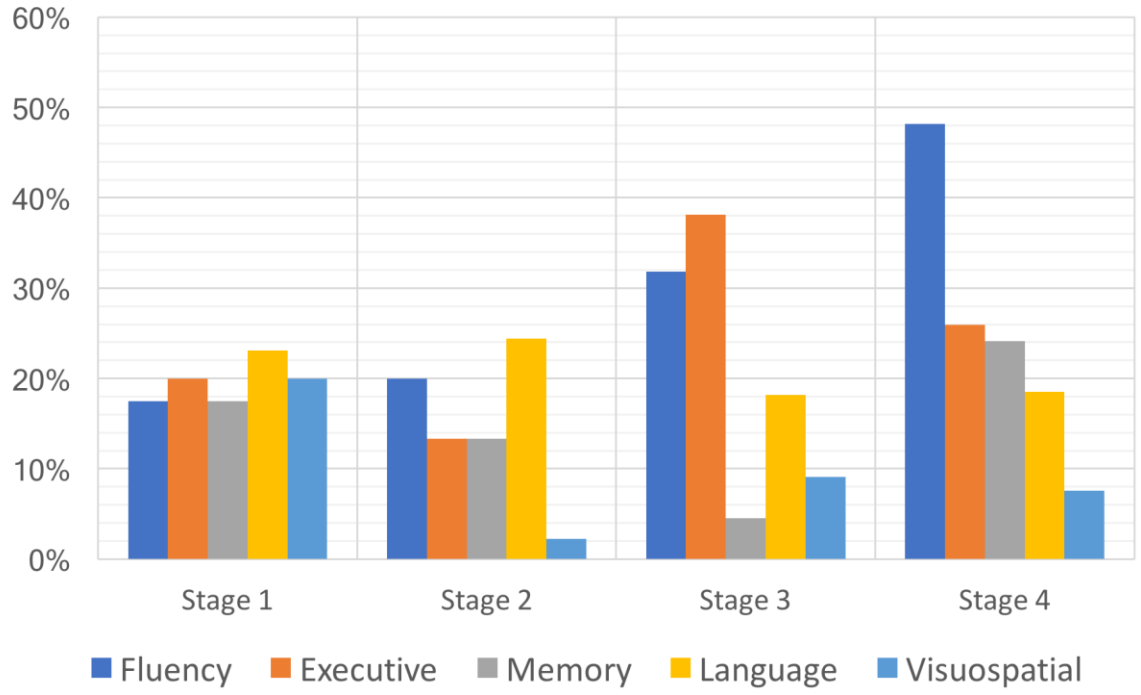
Table 4.4. Frequency of impairment across King's Clinical Disease Stages

	Stage 1[a]	Stage 2[a]	Stage 3[a]	Stage 4[a]	*Z*	*P*-value
ALS Specific	17.95	17.78	33.33	38.89	2.65	0.012
ALS Non-Specific	20.00	13.33	13.64	26.42	1.00	0.158
ECAS Total	20.51	20.00	33.33	39.62	2.24	0.050
Behaviour Impairment	17.65	26.83	36.36	65.39	4.77	< 0.001
Intact	57.58	53.65	57.14	19.61	-3.86	< 0.001

Note. [a] Values are percentages. P-Values corrected for multiple comparisons. Only patients with complete data reported (*n* = 146).

Patients with and without neuropsychological impairment were compared on demographic and clinical variables (described in Table 4.1) to determine which, if any, distinguish the groups. For demographic information, only education significantly differed between those patients with and without neuropsychological impairment ($t(123.93) = -2.44$, $p = .016$). However, after correcting for multiple comparisons this was no longer significant ($p = .065$). Regarding clinical features, anxiety ($W = 2941$, $p = .013$), depression ($W = 3359.5$, $p < .001$) and the ALSFRS-R ($t(133.92) = -3.55$, $p = .004$) significantly differed between groups. Thus, patients with neuropsychological impairment have higher levels of depression and anxiety, lower ALSFRS-R scores, and potentially fewer years of education.

Figure 4.3. Frequencies of impairment across King's Clinical Disease Stage for ECAS cognitive domains



4.4.3. Cognition, behaviour, and clinical variables

Clinical variables were analysed against ALS Specific, ALS Non-Specific, ECAS Total, and the number of behavioural features present (see see supplementary tables). A significant relationship was observed between the presence of bulbar involvement (but not site of onset) and ALS Specific functions (W = 3896.5, p = .033) and behaviour (W = 2061, p = .019). Patients were subdivided within each stage based on the presence or absence of bulbar involvement (see supplementary tables). Subsequent Jonckeere Terpstra Tests revealed that patients with evidence of bulbar involvement demonstrated a significantly worse ALS Specific (T_{JT} = 887, p = .021), ALS Non-Specific (T_{JT} = 956, p = .028), ECAS Total Score (T_{JT} = 875, p = .021), and behavioural features (T_{JT} = 1583, p < .001)

after correcting for multiple comparisons. Conversely, patients without bulbar signs demonstrated no significant relationship in cognitive or behavioural features.

Depression (r_s = .3560, p < .001) and the ALSFRS-R (r_s = -.258, p = .009) were related to behavioural features. To explore which behavioural domain was related to depression, depression scores of patients with and without each behavioural feature were compared. Significant differences, after correction, were observed for patients with and without apathy (W = 1043, p < .001), disinhibition (W = 773.5, p = .018), and loss of sympathy/empathy (W = 1036, p < .001). No significant relationship was observed between cognition or behaviour and site of onset, diagnostic delay, Riluzole use, weight (KG), upper limb involvement, lower limb involvement, or levels of anxiety.

4.5. Discussion

The aim of the present study was to determine the relationship between cognitive and behavioural symptoms, as measured using the ECAS, and the King's Clinical Staging system. In particular, the present study aimed to evaluate: a) whether cognition and behaviour is related to advancing disease stage in a clinically representative sample of ALS patients, b) which domains of cognition and behaviour are particularly related to disease stage, and c) which, if any, clinical variables relate to cognition and behaviour in ALS.

Our findings demonstrated that cognitive domains which are typically affected in ALS (ALS Specific), the ECAS Total performance, and the number of reported behavioural features significantly relate to King's Clinical Disease

Stages. Conversely, no such association was observed for cognitive functions not typically affected by ALS (i.e., memory and visuospatial functioning). Behavioural impairment as defined by the newly updated Strong criteria (Strong et al., 2017) also related to disease stage, with all five ECAS behavioural domains demonstrating increasing impairment in more advanced stages. These findings demonstrate that ALS Specific cognitive functioning and behaviour are significantly and negatively related to advancing disease stage. This relationship is driven most strongly by letter fluency performance, with executive dysfunction possibly also playing a role and global behavioural changes across all types of behaviour which characterise bvFTD (Raskovsky et al., 2011).

Structural and functional neuroimaging has shown that changes in ALS include extramotor areas that are involved in higher order cognitive processing and behavioural control (see Chiò et al., 2014 for overview). Executive functioning (including social cognition), fluency, and language have been associated with dysfunction of frontal and temporal regions of brain. For example, executive functioning and social cognition in ALS has been related to prefrontal dysfunction in ALS (Carluer et al., 2015; Pettit et al., 2013), with white matter tract connectivity also implicated (Abrahams et al., 2005b; Agosta et al., 2013; Canosa et al., 2016; Sarro et al., 2011). Letter fluency is a sensitive marker of cognitive impairment in ALS and has similarly been linked to prefrontal dysfunction (Abrahams et al., 2004, Pettit et al., 2013). Neuropsychological studies have shown that letter fluency impairment may represent a difficulty in cognitive initiation (e.g., Abrahams et al., 2000, Kasper et al., 2015) which in turn is related to the high frequency of apathy in ALS (Radakovic et al., 2017c). Similar to executive functioning and letter fluency, apathy has been associated with reduced fractional

anisotropy in the right anterior cingulate cortex (Woolley et al., 2011) and the dorsolateral and orbitomedial prefrontal cortex (Tsujimoto et al., 2011). Pathological TDP-43 inclusions have been suggested to spread predictably in ALS (Brettschneider et al., 2013), beginning in the primary motor cortex, spinal cord, and cranial nerves, spreading to the reticular formation of the brainstem, the prefrontal cortex, and finally the hippocampus. Executive and fluency dysfunction is commonly reported in ALS possibly due to early pathological involvement of the prefrontal cortex. However, memory dysfunction is less commonly reported, perhaps due to the exclusion of end-stage ALS patients from research studies (i.e., those with respiratory insufficiency). Indeed, memory impairment may be a feature of end stage ALS, but currently it is under-recognised. The strength of the relationship between behaviour and disease stage may suggest that behaviour is more susceptible to pathological disease spread than cognition. Higher rates of cognitive and behavioural dysfunction across disease stage therefore implicates progressive involvement of frontotemporal regions. However, given that respiratory dysfunction is one of the defining features of disease Stage 4, the late-stage involvement of ALS Non-Specific (e.g., memory) functions may be associated with declining respiratory function, which could be ameliorated by appropriately prescribed ventilatory support.

Previous cross-sectional and longitudinal research on cognition in ALS has been inconsistent as to whether cognition declines. Clinic-based studies have failed to reliably observe a relationship between cognition and disease progression (Abrahams et al., 2005a; Gordon, et al. 2010b; Schreiber et al., 2005). A large population-based longitudinal study from our group has previously

shown a relationship between the ALSFRS-R and cognition (Elamin et al., 2013). This inconsistency is most likely a function of sample sizes, high attrition rates, clinic versus population-based sampling, incident versus prevalence sampling, and the variability in metrics used to approximate disease progression (i.e., time or the ALSFRS-R).

As ALS is a heterogeneous condition with different disease trajectories, a system that defines progression based on clinical decline rather than as a function of time since first presentation is of greater utility when analysing disease progression. The King's Clinical Staging system is designed to overcome variability in disease trajectory over time. Our findings of a relationship between ALS Specific cognitive and behavioural change and King's Clinical Disease Stage provide additional evidence of spread of degenerative processes in the prefrontal cortices.

These findings have important clinical implications, with neuropsychological impairment previously associated with reduced survival (Elamin et al., 2011, Govaarts et al., 2016), quality of life (Chiò et la., 2010; Goldstein, Atkins, & Leigh, 2002), caregiver burden (Burke et al., 2015; Lillo et al., 2012b), and the ability to manage and engage with life-prolonging interventions (Olney et al., 2005; Stukovnik et al., 2010). It is therefore possible that quality of life and caregiver burden may also relate to disease stage. Clinically, it may be necessary to consider intervention programmes for caregivers to alleviate the impact of neuropsychological impairment, particularly early in the disease course. Furthermore, clinicians should be cognizant of current neuropsychological status when prescribing life-prolonging interventions to patients, and implement support structures for those with a neuropsychological

impairment e.g., providing instructions in simple written or pictorial format to reduce cognitive burden. The relationship between disease stage and behaviour is of particular importance, given the strength of this relationship relative to cognition and its negative impact on patients and caregivers. Behaviour change is less commonly reported in the literature compared to cognition, and often reported as a unidimensional construct. The profile and impact of behavioural change merits further and more detailed investigation in the future. Thus, the monitoring of both cognitive and behavioural symptoms across the disease course is vital to providing appropriate and timely care and support to patients with ALS and their families.

Consequently, the recently updated UK National Institute for Health and Care Excellence (NICE, 2016) guidelines on motor neuron disease assessment and management has incorporated cognitive and behavioural assessment as integral factors in patient care. Furthermore, the majority of ALS patients and caregivers have expressed their desire to be informed about the risk of neuropsychological impairment from their physician (Wicks & Frost, 2008). We have found that 80% of patients in King's Stage 4 experience cognitive or behavioural impairment. The relatively low frequency of cognitively intact patients argues in favour of incorporating cognitive and behavioural screening as a standard measure in ALS assessment.

We found no significant relationship between cognition, behaviour and diagnostic delay, Riluzole use, weight at testing, upper limb involvement, or lower limb involvement. However, the present findings suggest that bulbar involvement (but not site of onset) significantly relates to cognitive and behavioural performance. The relationship between the presence of bulbar symptoms and

cognition has been suggested previously (Abrahams et al., 1997). This may, in part, explain the slightly better performance in Stage 2 compared to Stage 1, in which a lower than expected proportion of bulbar onset patients were found. As such, the relationship between cognition, behaviour, and disease stage may be exaggerated by the presence of bulbar symptoms. Levels of depressive symptoms significantly related to behavioural functioning. There may be some overlap between symptoms of depression and behavioural abnormalities, specifically apathy. However, in the present study higher depression rates were also found in those patients with other behavioural abnormalities, specifically loss of sympathy/empathy, and disinhibited behaviour. It is possible that depressive symptoms and behavioural features occur concurrently, but further research is required to explore this relationship.

Stage 4 may represent a prognostic disease stage without the same degree of underlying pathology of Stages 1-3. However, removal of patients in Stage 4 without the clinical features of Stage 3 results in little change to the outcomes of this study. Certainly, respiratory insufficiency is a key feature of Stage 4 and 85% of patients in this stage showed respiratory involvement. Given that the defining characteristics of Stage 4 are respiratory insufficiency or feeding intervention because of nutritional deficiency, both of which may have secondary confounding effects on cognition, data were analysed for Stages 1 to 3 separately. The results indicated no significant difference between stages on either cognitive or behavioural measures. This may be because Stage 4 data are driving the effect as appears to be most likely in the behavioural data. Yet, it is important to note that the Jonckheere-Terpstra and Cochran-Armitage tests are both based on the assessment of a monotonic effect. The pattern of results for

Stages 1-3 appear curvilinear, and therefore the analyses lack the necessary power to detect an effect, and the decline from Stages 2 to 3 is not sufficient to overcome the removal of Stage 4.

Strengths of this study include its prospective multi-centre design, with a large sample size, and a clinically representative sample. As such, the results of this study possess good generalisability. However, an important limitation to this study is its cross-sectional design. This restricts the ability to fully explore how cognitive and behavioural symptoms evolve as patients transition to later stages of the disease. To do so, a longitudinal study is required to track patients' cognitive and behavioural performance in line with disease progression. Additionally, it is possible that patients with lower cognitive functioning and more severe behavioural abnormalities may have been less likely to participate. As such, it may be that the present results underestimate the prevalence of neuropsychological impairment across disease stages.

Cognitive and behavioural impairment is common in patients with ALS and present in all stages of the disease. ALS Specific functions (executive, language, and fluency) and behaviour are associated with clinical stage as defined by the King's Staging system, whereas ALS Non-Specific (memory, visuospatial) are not. Measures of cognitive and behavioural change should be included in the diagnostic criteria for ALS, and should be incorporated in future staging systems.

In Chapter 4 it was established that neuropsychological function in ALS is critically related to disease stage. Cross-sectionally, this provides evidence that cognition and behaviour may decline over the course of the disease. However, to evaluate this hypothesis, a longitudinal investigation of patient trajectories is required. Thus, Chapter 5 reports a longitudinal study of ALS patients, their caregivers, and control participants with regard to cognitive and behavioural functioning. By monitoring neuropsychological function as patients progress to more advanced disease stages, the relationship between cognition, behaviour, and disease stage can be elucidated.

CHAPTER 5: Longitudinal changes in ALS cognition and behaviour

5.1. Introduction

While research on the nature of neuropsychological symptoms in ALS is vast, studies exploring longitudinal changes are less so. As discussed in Section 1.10.2., findings from longitudinal studies of cognition in ALS have been mixed, with some reporting a significant decline and others reporting no significant change, or even improvement (Abrahams, Leigh, & Goldstein, 2005a; Gordon et al. 2010b; Schreiber et al. 2005). One large population-based study found that cognitive performance declines over time and that this decline is related to functional decline (Elamin et al., 2013).

Numerous methodological issues exist within the literature limiting the reliability of previous findings. Research has been limited by the use of tests dependent on motor speed, without adequate accommodations (e.g., Gordon et al., 2010b) and the repeated use of the same cognitive test; small sample sizes of often only 19-52 participants (Abrahams et al., 2005a; Gordon et al., 2010b; Kilani et al., 2004; Robinson et al., 2006; Schrieber et al., 2005; De Silva et al., 2016); a single follow-up time point (Abrahams et al., 2005a; Robinson et al., 2006; De Silva et al., 2016); or no appropriate control group (Gordon et al., 2010b; Schrieber et al., 2005; De Silva et al., 2016). Small sample sizes reduce the power to detect change, while the use of the same cognitive test over time may result in performance improvement due to learning test content or test-taking

strategies. This has the potential to mask longitudinal decline in ability, or even suggest improved functioning.

Attrition is of real concern in longitudinal cognitive research in ALS. For instance, Elamin et al. (2013) reported attrition at each study wave averaging 59% (n_1 = 186, n_2 = 98, n_3 = 46, n_4 = 11). Attrition averaged 28% (n_1 = 52, n_2 = 32, n_3 = 24, n_4 = 19) for Schreiber et al., (2005), and 49% (n_1 = 40, n_2 = 24, n_3 = 10) for Burkhardt et al., (2017). Similarly, De Silva et al., (2016) lost 60% of participants after baseline assessment (n_1 = 47, n_2 = 19). Yet, no study to date has controlled for attrition in its analysis, introducing significant bias. Elamin et al. (2013) observed that cognitive impairment was a significant predictor of attrition, suggesting that patients with lower neuropsychological functioning are less likely to continue participating. Data is therefore collected from only the few most cognitively able participants in available longitudinal research.

Measurement of disease progression in ALS can also be problematic due to the heterogeneous rate of decline. For instance, disease duration of ALS is approximately 3-4 years from onset and can range from 4 months to 23 years (Roche et al., 2012). The ALSFRS-R has been utilised previously as a marker of disease progression, with some cross-sectional studies reporting that cognitive and behavioural symptoms are related to a decline in functional ability (e.g., Gordon et al., 2010b, Murphy et al., 2016). Yet, decline on the ALSFRS-R is also heterogeneous and curvilinear, declining more rapidly in the early and late phases of the disease (Gordon & Cheung, 2006; Gordon et al., 2010a). Fortunately, the King's Clinical Disease Staging system has demonstrated good prognostic utility, and provides a linear and standardised metric of progression and burden (Roche et al., 2012; Balendra et al., 2015; Ferraro et al., 2016).

Two cross-sectional studies have explored the effect of disease stage on cognition and behaviour. One study found that executive and memory functioning significantly differed when patients are grouped by disease stage (Trojsi et al., 2016). However, this study was cross-sectional, did not include a measurement of behavioural dysfunction, and utilised an extensive battery of cognitive tests that do not control for motor disability resulting in a proportion of patients being unable to complete the cognitive assessments. Burke et al., (2017) found a cross-sectional relationship between behaviour and disease stage, however this relationship was not explored in-depth and the study did not provide information as to which behaviours related to clinical stage. We overcame some of these limitations in Chapter 4 in the utilisation of the ECAS and the analysis of individual behavioural domains. It was demonstrated that ALS Specific cognitive functions and all behaviour domains are related to clinical disease stage cross-sectionally (Crockford et al., 2018), such that by end-stage disease, approximately 80% of patients were neuropsychologically impaired. However, the effect of disease stage on cognition and behaviour has not been examined longitudinally.

In addition to King's Clinical Disease Stage, cognitive performance has been associated with fewer years of education (Beeldman et al., 2016; Elamin et al., 2011; Gordon et al., 2011; Massman et al., 1996; Montuschi et al., 2015; Murphy et al., 2016; Phukan et al., 2012) and older age of onset (Elamin et al., 2011; Montuschi et al., 2015; Murphy et al., 2007; Murphy et al., 2016; Phukan et al., 2012). The C9orf72 hexanucleotide repeat expansion is a significant contributor to both ALS and FTD, and has similarly been associated with cognitive and behavioural functioning (Ratti et al., 2012; Snowden et al., 2013), a higher prevalence of concomitant FTD in ALS (Byrne et al., 2012; Montuschi et al.,

2015), and a longitudinal decline in verbal fluency (Irwin et al., 2013). Therefore, these variables may play an important role in the longitudinal trajectory of ALS neuropsychological functioning.

Moreover, how change in different cognitive and behavioural domains relate to one another has yet to be explored; for instance, whether a decline in executive functioning relates to a decline in memory functioning, or whether a decline in fluency relates to increased probability of apathy. Previous research has shown that not all patients with ALS experience neuropsychological changes. As such, there exists apparent subgroups of patients who do and do not experience cognitive and behavioural impairment and decline. This is of clinical significance in order to provide accurate prognostic information to patients on what to expect of the disease, and in informing clinical care.

The present study aimed to build on the findings of Chapter 4 to examine longitudinal changes in cognition and behaviour in ALS using appropriately specified models, while accounting for covariates that may be related to rates of decline.

5.1.1. Aims

1) Examine the effect of neuropsychological impairment and disease stage/severity on attrition
2) Examine longitudinal changes in cognition and behaviour over time using appropriately specified models which control for attrition
3) Examine the effect of age of onset, years of education, the presence of C9orf72 repeat expansion, and King's Clinical Disease Stage on longitudinal cognitive and behavioural change.
4) Longitudinally verify the cross-sectional relationship between cognition, behaviour and disease stage presented in Chapter 4
5) Examine how longitudinal changes in cognitive and behavioural domains relate to one another
6) Investigate the presence of ALS cognitive and behavioural subgroups

5.2. Methods

5.2.1. Participants

Patients with ALS (*n* = 161) and control participants (*n* = 80) recruited into our previous cross-sectional investigation (Chapter 4) were followed longitudinally.

5.2.2. Procedure and Materials

Data collection procedures and materials for additional time periods follow procedures outlined in Chapter 4 (Crockford et al., 2018), with all assessments (except for socioeconomic status) administered at each time point. Participants

were assessed at four time points of 4 month intervals (± 1 month). To avoid the presence of practice effects in cognitive assessment, alternate versions of the ECAS (ECAS-A-B-C) were utilised in the present study sequentially (see Chapters 2 and 3). The alternate forms have shown to possess a high degree of equivalence, test-retest reliability, and inter-rater reliability (Crockford et al., 2017a; 2017b).

5.2.3. Statistical Analyses

Demographic, clinical, and neuropsychological data for the patient and control groups were compared using a χ^2 test for categorical data (or Fisher's exact test when expected cell frequencies fell below 5), Welch t-tests and one-way analyses of variance (ANOVA) with Holm-corrected Tukey's HSD post-hoc for continuous between group data, and Pearson or Spearman (as appropriate) correlation to explore the relationship between continuous/ordinal variables. When data violated statistical assumptions, log or power transformation were applied. When transformation failed to correct violations, non-parametric alternatives were used. Analyses were conducted using R 3.3.3 with alpha set to .05.

A cognitive deficit was determined using local validated abnormality cut-off scores from Scottish and Irish populations (Niven et al., 2015; Pinto-Grau et al., 2016). Behavioural impairment (ALSbi) was defined as the presence of two or more behavioural features on the ECAS Behaviour Screen, or the presence of apathy, as described by the recent consensus guidelines (Strong et al., 2017).

5.2.3.1. Neuropsychological impairment, disease stage/severity, and attrition (Aim 1)

Aim 1: *Examine the effect of neuropsychological impairment and disease stage/severity on attrition*

Risk factors for attrition at each follow-up time point were evaluated with step-wise binomial logistic regression models using predictors from the immediately preceding time point. The ALSFRS-R and King's Clinical Disease Stage were included to examine the effect of disease stage/severity on attrition. Disease stage was added to the models as a linear and quadratic polynomial. Cognitive impairment (ECAS Total Score) and behavioural impairment were added in a separate model to explore whether neuropsychological functioning affects attrition, while controlling for age and years of education. Disease stage/severity (measured using time-specific ALSFRS-R scores and King's Clinical Disease Stage) and neuropsychological (measured using rates of ECAS Total impairment and behavioural impairment) variables were initially analysed separately (to examine their unique contribution) before being combined in to a single logistic model.

5.2.3.2. Latent growth curve models (Aims 2 and 3)

To examine longitudinal changes in cognition and behaviour Latent Growth Curve Models (LGCM) were estimated. The LGCM is a special case of structural equation modelling in which change in cognition and behaviour is modelled as a function of time (see Beaujean, 2014 for overview). Variables are described as manifest if they are directly observed and measured, while latent variables are not directly observed but are inferred from manifest variables. An individual

growth trajectory is fit for each participant (i.e., random effect). Mean latent (i.e., unobserved) intercepts and slopes are estimated based on the random (individual) growth parameters of each participant. The mean of the latent intercept is the point at which the latent slope crosses the *y*-axis, and as such, can be described as the model-implied baseline level when Time 1 is set to zero. LGCMs estimate a number of parameters which can be constrained, or estimated freely. Unconstrained LGCMs allow the latent and manifest variables to co-vary amongst each other. Latent variable models consist of endogenous (i.e., outcome) and exogenous (predictor) variables. The benefit of using LGCM over other methods (e.g., mixed effects modelling) is the ability to model the latent slope and latent intercept covariance, as well as information on the unexplained variance (i.e., error variance). The covariance is a description of whether there is a relationship between the intercept (baseline level) and slope (rate of change). LGCMs can also easily handle missing data, common in clinical research (Enders et al., 2011).

In addition to modelling cognition and behaviour over time, LGCMs allow the addition of covariates in the form of regression equations. Covariates may be time-invariant, in that they do not change over time (e.g., biological sex), or time-variant (e.g., age) which are time-dependent. The latent intercept and latent slope are regressed on time-invariant covariates which indicates the effect that covariates have the baseline level (intercept) or rate of change (slope). Conversely, the endogenous (outcome) variable for each time point is regressed on time-variant covariates, which provides a metric of the relationship between the covariate and the endogenous variable within each time point.

5.2.3.3. Model specification (Aims 2 and 3)

LGCM were estimated using the R-package Lavaan (Rosseel, 2012). Time was centred at baseline (i.e., Time 1 assessment) coded as 0, 1, 2, and 3 for Times 1-4. Quadratic growth factors were also modelled by the addition of a latent slope coded as 0, 1, 4, and 9. Model fit was evaluated using χ^2 goodness-of-fit and Root Mean Square Error of Approximation (RMSEA). The χ^2 is a discrepancy function which measures how well the model-implied covariances match the observed sample covariances. A non-significant χ^2 value indicates no significant discrepancies between model-implied and sample covariances. The RMSEA is a parsimony index of model fit which takes account of model complexity. It measures whether the model reasonably approximates the data, with values closer to zero indicating better fit (Beaujean, 2014) with a p-value testing the hypothesis that RMSEA is less than or equal to .05 (i.e., close fit). Missing data were handled using Full Information Maximum Likelihood estimation. Residual variances were constrained to zero when they were negative within the model (estimation instability caused by the proximity of the true estimate to the boundary i.e., zero). Models with binary endogenous variables (e.g., presence/absence of apathy) are estimated using probit link functions. As such, model coefficients for binary data are expressed in terms of probit probability. To further control for potential practice effects (in addition to using alternate forms of the ECAS), patients' cognitive scores were converted into standardised z-scores based on the mean and standard deviation of local control groups (i.e., UK and Ireland).

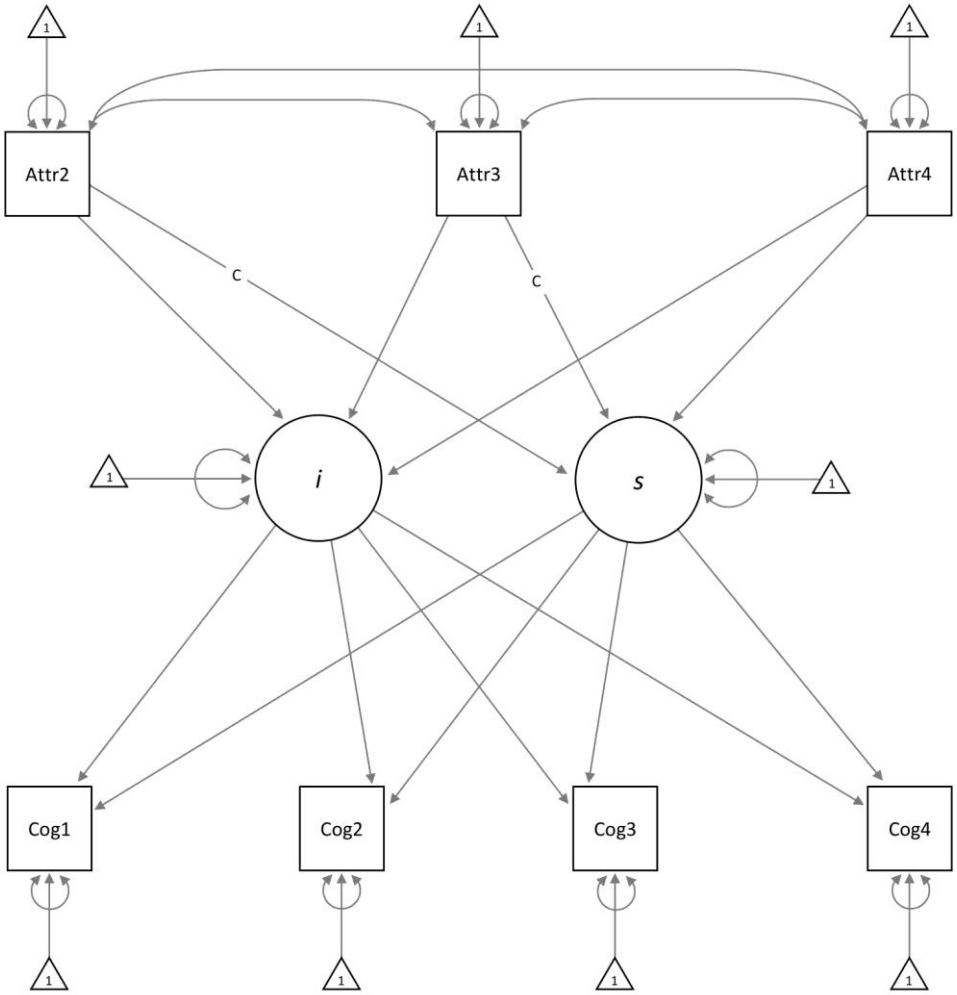
To address the Aims 2 and 3 of this chapter, longitudinal change in each cognitive and behavioural domain was examined using unconstrained LGCMs controlling for attrition in two steps: a) models examining change as a function of

time while controlling for attrition (Aim 2: *Basic LGCM*), and b) models containing both time-invariant and time-variant covariates (Aim 3: *Covariate LGCM*).

Aim 2: *Examine longitudinal changes in cognition and behaviour over time using appropriately specified models which control for attrition*

Longitudinal change in cognition and behaviour were examined using unconstrained LGCMs, termed 'Basic LGCM' (Figure 5.1). These models examine the change in neuropsychological performance as a function of time, while controlling for attrition. To control for data *missing not at random* (i.e., attrition dependent on manifest variables), the Wu-Carroll selection model was employed (Wu & Carroll, 1988). The Wu-Caroll method assumes that attrition is a function of each participant's longitudinal trajectory, such that declining cognition is hypothesised to increase the probability of attrition. To incorporate the Wu-Carroll selection method for the LGCMs, the latent slope and latent intercept were regressed onto a dichotomous attrition variable (constrained to linearity), thus providing an estimate of cognitive and behavioural change over time corrected for biased drop-out (see Enders et al., 2011 for discussion).

Figure 5.1. Path diagram of Basic LGCM (Aim 2)

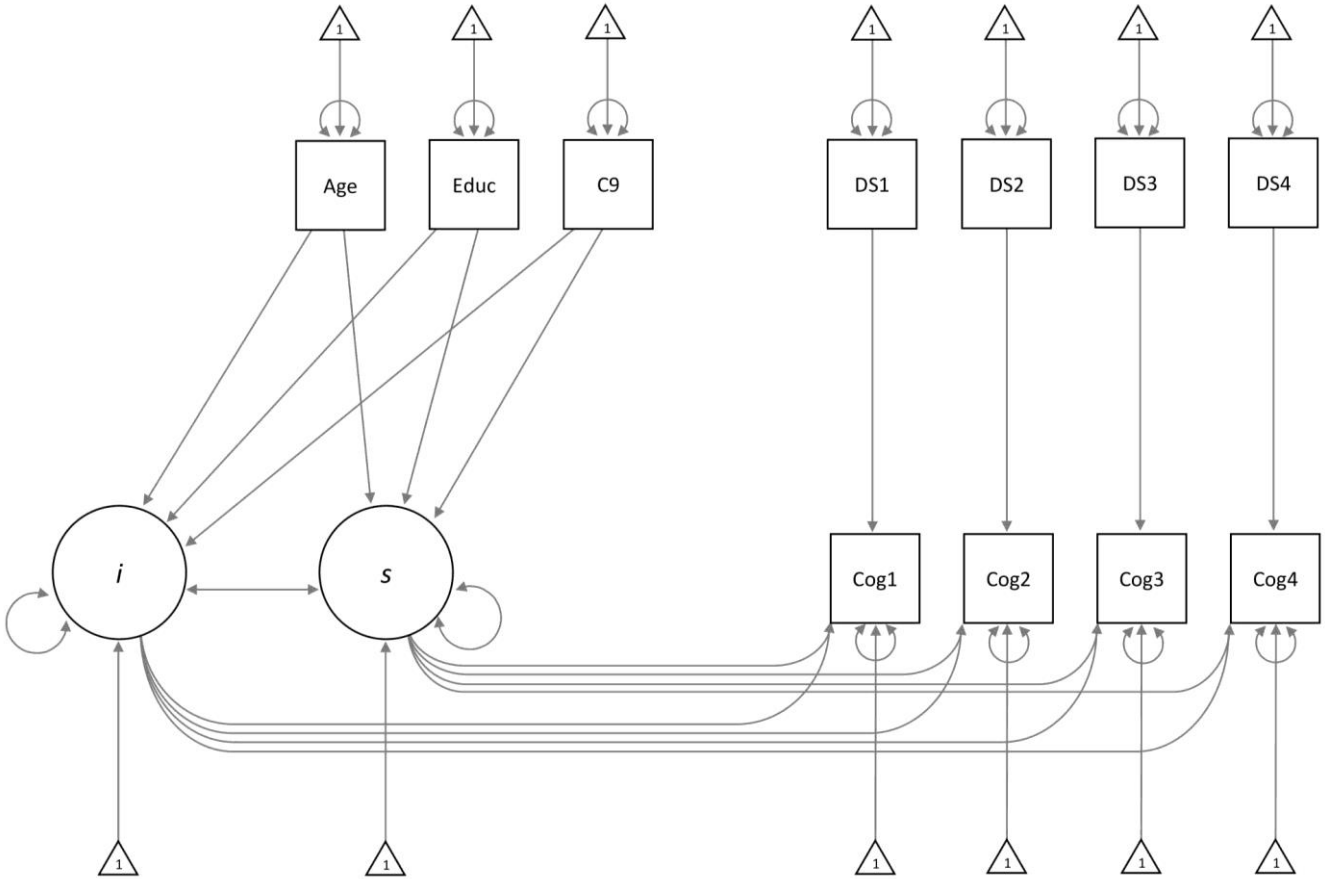


Note. Prototypical path diagram for unconstrained latent growth curve model controlling for attrition. Attr2-Attr4 = attrition variable (binary) for Times 2 to Time 4; *i* = intercept (latent); *s* = slope (latent); Cog1-Cog4 = cognitive outcome for Time 1 to Time 4. Ellipses represent latent variables while squares represent manifest variables. Single-headed arrows represent regression coefficients. Double-headed arrows represent variance when restricted to one variable, and covariance when between two variables. Triangles represent means for latent and manifest variables. C = addition of constant to constrain relationship to be linear.

Aim 3: *Examine the effect of age of onset, years of education, the presence of C9orf72 repeat expansion, and King's Clinical Disease Stage on longitudinal cognitive and behavioural change.*

The evaluation of Aim 3 is achieved by building on from the Basic LGCM of Aim 2 with the incorporation of time-invariant and time-variant covariates (Covariate LCGM; Figure 5.2). Time-invariant covariates used in this study are age of onset, years of education, and the presence of C9orf72 repeat expansion. The time-variant covariate is King's Clinical Disease Stage at each time point. The latent intercept and latent slope are regressed on age of onset, years of education, and C9orf72 status, which indicates the effect that these covariates have the baseline level (intercept) and rate of change (slope). The endogenous variable (ECAS cognitive and behavioural domains) for each time point is regressed on King's Clinical Disease Stage indicating whether disease stage significantly relates to cognition/behaviour within each time point. Changes in parameter estimates from the Basic LGCM to the Covariate LGCM indicate the variance captured by the inclusion of model covariates.

Figure 5.2. Path diagram of Covariate LGCM (Aim 3)



Note. Prototypical path diagram for unconstrained latent growth curve model with covariates controlling for attrition; *i* = intercept (latent); *s* = slope (latent); Cog1-Cog4 = cognitive outcome for Time 1 to Time 4. DS1=DS4 = King's Clinical Disease Stage for Times 1 to 4. Age = age at onset. Education = years of education. C9 = C9orf72 status. Ellipses represent latent variables while squares represent manifest variables. Single-headed arrows represent regression coefficients. Double-headed arrows represent covariance. Triangles represent means for latent and manifest variables. C = addition of constant to constrain relationship to be linear. Covariances between manifest exogenous variables not shown in diagram. Attrition variables not shown in diagram but follow same relationship path as age of onset, education and C9. Numeric partition to latent slope regression paths represents time coding. Numeric partition to latent intercept regression paths represents constraints specifying that the latent intercept has equal influence on indicator variables across all time points.

Aim 4: *Longitudinally verify the cross-sectional relationship between cognition, behaviour and disease stage presented in Chapter 4*

King's Clinical Disease Staging is based on standardised proportions, such that each stage of the disease represents a standardised proportion of the disease course. While this provides a standardised measurement of disease progression relative to other metrics, individual patients do not necessarily progress at the same rate. For instance, 6 months for one patient may represent 50% of that individual's disease course with transition to more advanced disease stage. Conversely, 6 months for a different patient may only represent 20% of the disease course with no progression to a later disease stage. As such, it is not possible to estimate LGCMs of cognition and behaviour as a direct function of disease stage - rather than time - as patients may provide data for multiple time points but for a single disease stage.

Therefore, patient data were restructured to directly explore the longitudinal effect of disease stage on cognition and behaviour, and verify the results of Chapter 4 longitudinally. Mean average was calculated and used for cognitive scores for which multiple time points represent the same disease stage. For behavioural domains (e.g., presence of apathy), the presence of apathy at any time point within a disease stage is recorded. For instance, an ALS patient provides data for three time points and is in Stage 1 at Time 1, Stage 1 at Time 2, and Stage 2 at Time 3. The mean z-score for Times 1 and 2 is taken as their average score for Stage 1, while their score for Time 3 is taken as their score for Stage 2. This individual presented with apathy at Time 1 and Time 3, but not at Time 2. As such, they are marked as apathy present for Stage 1 and 2. Rates of impairment for disease stages were calculated from raw scores. The same

procedure described above was implemented, such that scores for cognitive domains within each disease stage were averaged. Impairment was determined from the average score within a disease stage based on locally validated cut-offs (Niven et al., 2015; Pinto-Grau et al., 2016).

For continuous data, standardised scores of cognitive domains were structured by disease stage were analysed using mixed-effects models. Initially, ECAS composite domains were analysed (ECAS Total, ALS Specific, ALS Non-Specific, behaviour score) followed by subdomains (e.g., executive functioning, fluency) when composite domains were found to be significant. The relationship between disease stage and the ECAS domains were modelled with linear, quadratic, and cubic polynomials. For categorical data (e.g., rates of impairment, presence of apathy), main effect analyses were conducted using Cochran–Mantel–Haenszel χ^2 test for matched categorical data. Post-hoc Cochran-Armitage tests were employed when a significant main effect was observed and subjected to Holm-Bonferroni correction for multiple comparisons.

Aim 5: *Examine how longitudinal changes in cognition and behaviour relate to one another*

To explore the inter-relationship of the ECAS cognitive and behavioural subdomains, hierarchical cluster analysis was performed. To examine which cognitive and behavioural domains decline at similar rates, model-implied random slopes from the basic LGCM of Chapter 5 were extracted and subjected to correlational analysis. Slopes from the basic models were utilised as the slopes from the covariate models are dependent on disease stage, age of onset, education, and C9orf72 status. Euclidean distances, the straight line distance

between two points in *n*-dimensional space, were calculated from the absolute values of the correlation coefficients. Complete-linkage clustering, an agglomerative approach, was performed in which each domain begins in its own cluster and is combined with sequentially larger clusters based on Euclidean distances. The slopes for behavioural domains were inverted such that a negative slope represents increasing longitudinal probability e.g., a positive correlation between cognition and behaviour is interpreted as 'a faster rate of decline in cognitive performance is related to an increased probability of behaviour'.

Aim 6: *Evaluate the presence of ALS cognitive and behavioural subgroups*

To identify potential patient subgroups, a similar procedure as Aim 4 was performed. LGCMs provide model-implied slopes, in addition to model-implied fitted values for each patient at each time point were extracted. Hierarchical complete-linkage clustering on model-implied slopes was conducted in which each patient begins in his or her own cluster, with patients combined sequentially into larger clusters. Clinical and demographic variables were compared between groups using analysis of variance.

5.3. Results

5.3.1. Demographic and clinical data

Clinical and demographic characteristics are presented in Tables 5.1. and 5.2. For the longitudinal data (Time 2, 3, and 4), no significant differences were observed except for HADS Depression at Time 4 (W = 862, p = .040). C9orf72

status was available for 100 patients, of whom, 8% tested positive (> 30 repeats). One patient tested positive for intermediate repeat expansion (24 repeats) and was treated as positive, bringing the total to 9%. This is in line with Gómez-Tortosa et al. (2013) who found that patients with expansions of 20-30 repeats had similar clinical phenotypes as those with longer expansions.

The mean interval between testing sessions was 4.4 months for patients and 4.40 months for controls. For patients, the mean interval for Time 1 to Time 2 was 4.4 months (± .86), 4.4 months (± .90) for Time 2 to Time 3, and 4.1 (± .76) for Time 3 to Time 4. For controls, the intervals were 4.4 (± .82), 4.0 (± .64), and 4.1 (± .49) respectively. Attrition was observed at each time point relative to the last (37.3% at Time 2, 32.7% at Time 3, and 33.8% at Time 4) and controls (27.5%, 12.1%, 29.4% respectively). Reasons for patient withdrawal include: declining further participation (*n* = 76), death (*n* = 21), and inability to contact (*n* = 20). For control participants, an inability to make contact (*n* = 29) and declining participation (*n* = 15) resulted in attrition.

Table 5.1. Demographics variables by time

	Time 1			Time 2			Time 3			Time 4		
	ALS (*n* = 161)	Control (*n* = 80)	*p*	ALS (*n* = 101)	Control (*n* = 58)	*p*	ALS (*n* = 68)	Control (*n* = 51)	*p*	ALS (*n* = 42)	Control (*n* = 36)	*p*
Gender (% Male)	67.1	60.0	.890	71.3	62.1	.890	72.1	60.8	.890	71.43	55.6	.890
Age	61.39 ± 11.58	60.83 ± 13.23	.999	60.45 ± 11.90	62.33 ± 13.32	.999	59.65 ± 12.69	62.49 ± 13.57	.990	58.71 ± 11.03	60.78 ± 14.40	.999
Education	13.93 ± 3.52	14.49 ± 3.31	.491	14.09 ± 3.29	14.48 ± 3.17	.491	14.1 ± 3.14	15.03 ± 3.18	.466	14.20 ± 2.85	15 ± 3.31	.491
SES†	2 ± 1.48	2 ± 1.48	.300	2 ± 1.48	1 ± 0	.300	2 ± 1.48	1 ± 0	.300	3 ± 2.22	2 ± 1.48	.300
Anxiety†	4 ± 2.97	3.5 ± 2.22	.761	3 ± 2.97	3 ± 2.97	.761	3 ± 2.97	3 ± 2.97	.746	2 ± 2.97	3 ± 2.97	.746
Depression†	1 ± 1.48	1 ± 1.48	.171	1 ± 1.48	1 ± 1.48	.999	1 ± 1.48	1 ± 1.48	.999	2 ± 1.48	1 ± 1.48	.040

Above corrected for multiple comparisons (Holm-Bonferroni correction, 4 comparisons). † = median ± median absolute deviation, Wilcoxon Rank Sum Test. Depression and Anxiety measured using the Hospital Anxiety and Depression Scale.

Table 5.2. Clinical variables by time

	Time 1 *n* = 161	Time 2 *n* = 101	Time 3 *n* = 68	Time 4 *n* = 42
Age at onset	59.43 ± 11.75	57.99 ± 12.17	56.53 ± 12.86	55.33 ± 11.27
Diagnostic Delay (months)†	11 ± 7.41	12 ± 8.9	12 ± 8.9	12 ± 7.41
Time since onset (months)†	16 ± 11.86	20 ± 10.38	24 ± 10.38	28 ± 8.9
Riluzole (% Yes)	75.8	80.2	79.4	83.3
ALSFRS-R	38.28 ± 6.94	34.98 ± 8.13	32.66 ± 8.44	34.08 ± 7.38
C9orf72	9%	5.8%	6.3%	10 %
King's Disease Stage (1/2/3/4; %)	25/28/14/34	13/25/16/47	10/16/22/52	7/14/21/57
MITOS Stage: (0/1/2/3/4 %)	71/21/7/1/0	63/26/8/2/0	49/34/15/0/2	47/31/22/0/0
Site of onset (B/UL/LL/R/M; %)	26/29/35/1/9	20/36/33/2/10	13/40/32/2/13	7/43/36/2/12
Regions involved:				
Bulbar (% Yes)	51.6	56.4	67.2	75
Upper limb (% Yes)	72.1	87.1	92.5	95
Lower limb (% Yes)	72.7	84.2	92.5	95
Respiratory (% Yes)	29.2	43.6	48.5	57.1

Note. B = Bulbar, UL = Upper limb, LL = Lower limb, R = Respiratory, M = mixed onset. MITOS Time 1 (*n* = 150), Time 2 (*n* = 87). Time 3 (*n* = 61), time 4 (*n* = 32). Genetic testing Time 1 (*n* = 100), Time 2 (*n* = 69), Time 3 (*n* = 48), Time 4 (*n* = 30). King's Clinical Disease Stage information missing for two patients in Time 4. † = median ± median absolute deviation.

5.3.2. Cognition: Comparison between patients and controls

The domains of the ECAS (language, fluency, executive, memory, and visuospatial) in addition to the composite score (ALS Specific, ALS Non-specific, and ECAS Total) were compared between patients and controls at each time point (See Table 5.3). Significant differences (corrected for multiple comparisons) in ALS-Specific (Time 1: $t(216.64) = -5.12$, $p < .001$; Time 2: $t(155.64) = -4.05$, $p < .001$; Time 3: $t(114.24) = -2.77$, $p = .013$; Time 4: $W = 516$, $p = .016$), ALS Non-specific (Time 1: $t(213.72) = -4.89$, $p < .001$; Time 2: $t(143.63) = -2.21$, $p = .046$; Time 3: $t(114.59) = -2.72$, p = .027; Time 4: $W = 530$, $p = .046$), and ECAS Total Scores (Time 1: $t(212.07) = -5.49$, $p < .001$; Time 2: $W = 1921$, $p = .001$; Time 3: $W = 1077.5$, $p = .001$; Time 4: $W = 484.5$, $p = .007$) were present across all four time points. Language functions between patients and controls significantly differed for Time 1 ($W = 4614$, $p < .001$), Time 2 ($W = 2182$, $p = .012$), and Time 3 ($W = 1194.5$, $p = .009$). Fluency differed for Time 1 ($t(232.43) = -5.34$, $p < .001$), Time 2 ($W = 1894.5$, $p = .001$), and Time 3 ($W = 1239$, $p = .01$). Executive functions differed for Times 1 ($t(202.24) = -4.24$, $p < .001$) and Time 2 ($t(153.87) = -3.29$, $p = .004$), while memory functions differed for Time 1 ($t(213.64.43) = -5.11$, $p < .001$), Time 2 ($t(143.19) = -2.38$, $p = .037$), and Time 3 ($t(116.15) = -2.71$, $p = .024$). No significant differences were observed for visuospatial functioning at any time point. Examination of mean raw scores suggest no changes in cognitive or behavioural functioning over time, with rates of impairment appearing to reduce over time. Rates of neuropsychological impairment are presented in Table 5.4.

Table 5.3. Cognition and behaviour functioning over time

	Time 1			Time 2			Time 3			Time 4		
	ALS *n* = 161	Control *n* = 80	*p*	ALS *n* = 101	Control *n* = 58	*p*	ALS *n* = 68	Control *n* = 51	*p*	ALS *n* = 42	Control *n* = 36	*p*
Cognition												
ECAS Total	104.07 ± 16.59	114.24 ± 11.65	<.001	108.54 ± 16.17	116.52 ± 10.68	.001	109.94 ± 13.58	116.73 ± 11.15	.001	110.36 ± 15.69	117.17 ± 11.4	.007
ALS Specific	76.71 ± 13.44	84.26 ± 9.12	<.001	79.88 ± 12.9	86.57 ± 7.83	<.001	81.51 ± 10.06	86.31 ± 8.79	.013	81.48 ± 11.87	86.25 ± 9.31	.016†
Language	27.00 ± 1.48	28.00 ± 0	<.001†	27.00 ± 1.48	27.00 ± 1.48	.012†	26.00 ± 2.97	27.00 ± 1.48	.009†	27.00 ± 1.48	27.00 ± 1.48	.066†
Fluency	16.32 ± 5.02	19.07 ± 2.95	<.001	17.78 ± 4.57	20.03 ± 1.93	<.001†	18.26 ± 4.07	19.8 ± 2.97	.01†	18.48 ± 3.95	19.50 ± 3.04	.200
Executive	34.44 ± 7.84	38.27 ± 5.89	<.001	36.33 ± 8.05	39.83 ± 5.32	.004	37.69 ± 6.08	39.75 ± 5.68	.117	37.07 ± 7.87	40.00 ± 5.51	.117
ALS Non-Specific	27.04 ± 5.41	29.98 ± 3.76	<.001	28.47 ± 4.73	29.95 ± 3.65	.046	28.43 ± 4.84	30.41 ± 3.11	.023	28.88 ± 5.14	30.92 ± 3.39	.046
Memory	15.48 ± 4.94	18.27 ± 3.43	<.001	17.19 ± 4.02	18.55 ± 3.12	.037	17.12 ± 4.22	18.88 ± 2.89	.024	17.26 ± 4.68	19.08 ± 3.41	.051
Visuospatial*	12.00 ± 0	12.00 ± 0	.542†	12.00 ± 0	12.00 ± 0	.999†	12.00 ± 0	12.00 ± 0	.999†	12.00 ± 0	12.00 ± 0	.942†
Behaviour												
	n = 149			*n* = 92			*n* = 61			*n* = 24		
Dimensions % (0/1/2/3+)	45.0 / 21.5 / 14.1 / 19.5			47.8 / 23.9 / 14.1 / 14.1			44.3 / 26.2 / 11.5 / 18.0			54.2 / 12.5 / 8.3 / 33.33		
Apathy %	30.9			29.3			39.3			29.2		
Disinhibition %	15.4			14.1			18			8.3		
Empathy %	27.5			23.9			26.2			20.8		
Perseveration %	24.8			21.7			29.5			33.3		
Hyperorality %	24.8			17.4			9.8			16.7		
Psychosis %	6.7			4.4			3.3			4.2		

Note. † = non-parametric Mann-Whitney, median and MAD reported. P-values corrected for multiple comparisons (Holm-Bonferroni; comparisons = 4)

Table 5.4. Rates of neuropsychological impairment by time

	Time 1 % (*n*)	Time 2 % (*n*)	Time 3 % (*n*)	Time 4 % (*n*)
ECAS Total	28.5 (158)	20.0 (100)	16.2 (68)	14.3 (42)
ALS Specific	27.0 (159)	22.0 (100)	19.1 (68)	19.1 (42)
Language	21.3 (160)	28.0 (100)	32.4 (68)	38.1 (42)
Fluency	30.4 (161)	16.0 (100)	10.3 (68)	14.3 (42)
Executive	22.5 (160)	18.8 (101)	8.8 (68)	16.7 (42)
ALS Non-Specific	19.4 (160)	12.9 (101)	14.7 (68)	4.8 (42)
Memory	16.8 (161)	9.9 (101)	11.8 (68)	7.1 (42)
Visuospatial	9.4 (160)	11.9 (101)	13.2 (68)	7.1 (42)
Behaviour Impairment	39.6 (149)	35.9 (92)	42.6 (61)	33.3 (24)

Note. Behaviour Impairment measured using the ECAS Behaviour Screen and defined by Strong et al., (2017) consensus guidelines.

5.3.3. Neuropsychological impairment, disease stage/severity, and attrition (Aim 1)

Aim 1: *Examine the effect of neuropsychological impairment and disease stage/severity on attrition*

The influence of disease stage/severity and neuropsychological status on attrition was explored using binomial logistic regression models. Disease stage/severity variables (ALSFRS-R and King's Clinical Disease Stage) significantly predicted attrition at Time 2 ($X^2(4) = 11.96$, $p = .018$), with the ALSFRS-R significant within the model (*OR* = .94, 95% *CI*: .88 - .99, $p = .042$) suggesting that a higher ALSFRS-R score (better physical function) is related to an increased likelihood to participate. Disease severity variables did not significantly relate to attrition at Time 3 ($X^2(4) = 5.83$, $p = .212$) or Time 4 ($X^2(4) = 7.45$, $p = .114$).

The neuropsychological variables model (age, education, ECAS Total impairment, and behaviour impairment) was significant for Time 2 ($X^2(4) = 17.12$, p = .002). Within the model, older age (*OR* = 1.04, 95% *CI*: 1.00 – 1.08, *p* = .034) and the presence of behavioural impairment (*OR* = 2.64, 95% *CI*: 1.25 – 5.69, *p* = .012) were significant, relating to increased likelihood of attrition. For Time 3, cognitive impairment was significantly related to increasing probability of attrition (*OR* = 3.89, 95% *CI*: 1.11 – 14.96, *p* = .038) within the model, however, the overall model was not significant ($X^2(4) = 6.05$, *p* = .195). For Time 4, neuropsychological impairment did not significantly predict attrition ($X^2(4) = 1.25$, p = .870).

The combined model, including disease stage/severity and neuropsychological status, was significant for Time 2 ($X^2(8) = 23.97$, *p* = .002), with age uniquely significant (*OR* = 1.04, 95% *CI*: 1.01 – 1.09, *p* = .028). For Time 3, cognitive impairment was a significant predictor (*OR* = 5.36, 95% *CI*: 1.18 – 28.55, *p* = .036), but the overall combined model did not significantly predict attrition ($X^2(8) = 8.73$, *p* = .366). At Time 4, age was significant (*OR* = 1.09, 95% *CI*: 1.02 – 1.20, *p* = .031), but the overall model did not significantly predict attrition ($X^2(8) = 13.38$, *p* = .099). Therefore, progressive physical disability, older age, and the presence of cognitive or behavioural impairment are significantly related to increased likelihood of attrition at different time points. As such, it is necessary to account for attrition in longitudinal models of ALS patients' cognitive and behavioural performance.

5.3.4. Latent Growth Curve Models (LGCM; Aim 2 and 3)

5.3.4.1. Evaluation of model fit

Model fit indices for LGCMs of cognitive variables are presented in Table 5.5. Model fit of the attrition-controlled models (Basic LGCM) was poor for ALS Non-Specific and memory domains, with significant χ^2 goodness of fit and RMSEA values. Reasonable fit was observed for ECAS Total, ALS Specific, and language with significant χ^2 values but a non-significant RMSEA. Model fit for fluency, executive, and visuospatial functions was good. One outlier was removed from the visuospatial model. Negative residual slope variance was observed for language and visuospatial functions which were constrained to zero suggesting a lack of variability in rates of longitudinal change. The visuospatial functions model also possessed negative intercept variance. Therefore, the majority of cognitive models possessed good or reasonable model fit. Model fit for behavioural data was superior compared to the cognitive data. Only the behaviour score model was of poor fit with significant χ^2 and RMSEA values. However, a greater number of variables contained negative variances which were constrained to zero. Loss of sympathy/empathy and eating behaviours (hyperorality) possessed the best fit and specification. As such, model fit was good or acceptable for all cognitive and behavioural variables, except for ALS Non-Specific, memory functions, and behaviour score. The addition of quadratic growth factors negatively impacted the fit and specification of models, and as such, only linear growth factors were fit to data.

The addition of covariates (Covariate LGCM) improved the model fit for ECAS cognitive domains. Model fit for ECAS Total, ALS Specific, fluency, executive, and memory disease stage models was good with non-significant χ^2

and RMSEA indices. A significant χ^2 score was found for language and ALS Non-Specific, but only language functions had a concurrent significant RMSEA value. As such, model fit was poor for language functions and acceptable for ALS Non-Specific functions. Residual slope variance was constrained to zero for language and visuospatial, with slope variance for visuospatial functions also constrained. For behaviour, the addition of disease stage improved model fit for behaviour score. No behaviour domain had significant χ^2 and RMSEA values, except that the χ^2 (but not RMSEA) index was significant for disinhibition. Constraints on residual slope variance was placed on behaviour score, ALSbi, apathy, disinhibition, and perseveration.

Table 5.5. Model fit indices for Latent Growth Curve models of the ECAS

	Basic LGCM		Covariate LGCM	
	χ^2	RMSEA	χ^2	RMSEA
ECAS Total	**χ^2 (12) = 21.14, *p* = .048**	.069 (.006-.116), *p* = .209	χ^2 (30) = 34.29, *p* = .269	.030 (<.001-.069), *p* = .763
ALS Specific	**χ^2 (12) = 23.94, *p* = .021**	.079 (.030-.124), *p* = .140	χ^2 (30) = 27.46, *p* = .599	<. 001 (<.001-.053), *p* = .935
Language	**χ^2 (14) = 29.29, *p* = .010***	.082 (.039-.124), *p* = .097*	**χ^2 (32) = 64.13, *p* = .001***	**.079 (.050-.107), *p* = .048***
Fluency	χ^2 (12) = 19.85, *p* = .070	.064 (<.001-.112), *p* = .289	χ^2 (30) = 34.72, *p* = .253	.03 (<.001-.070), *p* = .749
Executive	χ^2 (12) = 7.56, *p* = .818	< .001 (<.001-.050), *p* = .950	χ^2 (30) = 20.94, *p* = .890	< .001 (<.001-.028), *p* = .992
ALS Non-Specific	**χ^2 (12) = 40.73, *p* < .001**	**.112 (.082-.164), *p* = .003**	**χ^2 (30) = 59.14, *p* = .001**	.078 (.048-.107), *p* = .061
Memory	**χ^2 (12) = 31.22, *p* = .002**	**.100 (.074-.143), *p* = .029**	χ^2 (30) = 40.48, *p* = .096	.047 (<.001-.080), *p* = .530
Visuospatial	χ^2 (15) = 14.41, *p* = .495*†	<.001 (<.001-.072) *p* = .813*†	χ^2 (33) = 29.15, *p* = .660*†	< .001 (<.001-.048), *p* = .957*†
Behaviour score	**χ^2 (15) = 92.50, *p* < .001*†**	**.179 (.145-.215), *p* < .001***	χ^2 (32) = 44.45, *p* = .071*	.049 (<.001-.081), *p* = .486*
ALSbi	χ^2 (14) = 12.75, *p* = .546*	< .001 (.030-.124), *p* = .140*	χ^2 (32) = 33.95, *p* = .374*	.019 (<.001-.063), *p* = .848*
Disinhibition	χ^2 (14) = 3.73, *p* = .997*	< .001 (<.001- .001), *p* > .999*	**χ^2 (32) = 50.54, *p* = .020***	.060 (.024-.090), *p* = .280*
Apathy	χ^2 (14) = 12.37, *p* = .576*	< .001 (<.001-.068), *p* = .854*†	χ^2 (32) = 34.99, *p* = .328*	.024 (<.001-.065), *p* = .820*
Sympathy/empathy	χ^2 (12) = 7.82, *p* = .799	< .001 (<.001 -.052), *p* = .943	χ^2 (30) = 38.32, *p* = .142	< .001 (<.001-.048), *p* = .615
Perseveration	χ^2 (14) = 2.38, *p* > .999*	< .001 (<.001- <.001), *p* > .999*	χ^2 (32) = 26.83, *p* = .726*	< .001(<.001-.045), *p* = .970*
Hyperorality	χ^2 (12) = 9.73, *p* = .640	< .001 (<.001-.067), *p* = .873	χ^2 (30) = 22.47, *p* = .096	< .001 (<.001-.036), *p* = .986

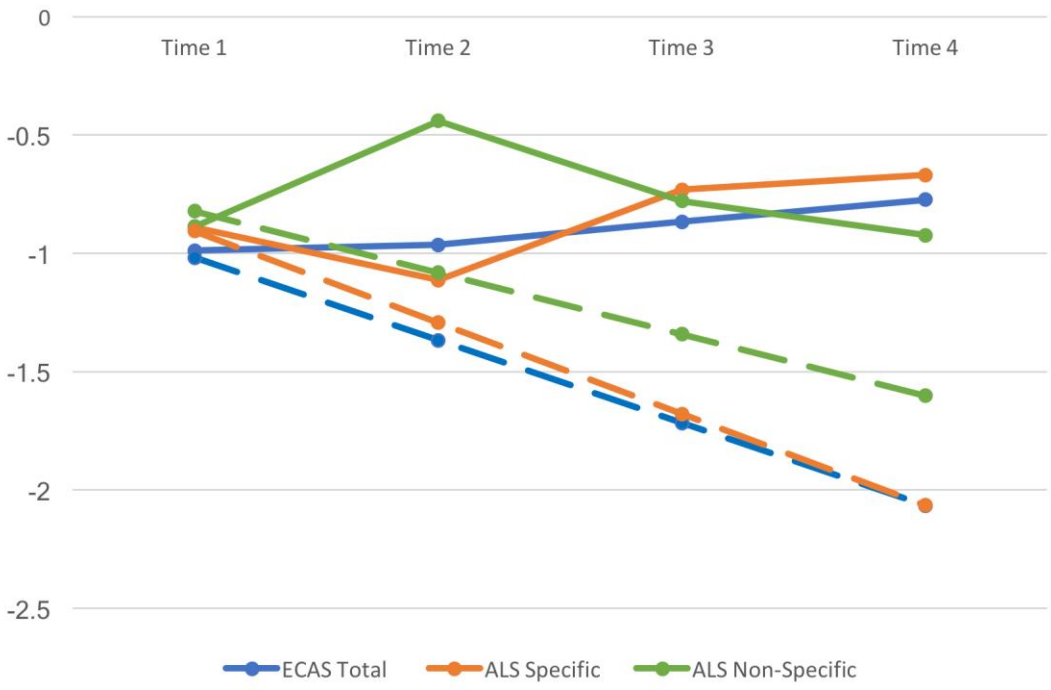
Note. χ^2 is the chi-square goodness of fit test, RMSEA (Root Mean Square Error of Approximation) 90% confidence interval presented in parenthesis. * Slope residual variance constrained to zero. † Intercept variance constrained to zero. When either slope or intercept is constrained, so too is the slope-intercept covariance constrained to zero.

5.3.5. Evolution of cognitive functioning over time (Aim 2)

Aim 2**:** *Examine longitudinal changes in cognition and behaviour over time using appropriately specified models which control for attrition*

Latent growth curve models were generated for each cognitive and behavioural domain of the ECAS (Table 5.6). Figure 5.3 displays the mean and model-implied means of the ECAS composite domains using the Wu-Carroll Selection method demonstrating the impact that controlling for attrition has on the trajectories of change.

Figure 5.3. Comparison of mean scores and model-implied means for ECAS composite scores



Note. Solid lines = mean scores; Dashed lines = model-implied means. Mean scores are the mean z-scores for cognitive functions at each time period. The model-implied means are taken from the LGCM controlling for attrition (Basic LGCM), demonstrating the bias introduced by not controlling for non-random attrition.

Cognition: Significant mean latent intercepts were observed for the ECAS Total Score, ALS Specific, and ALS Non-Specific models suggesting a significant deviation in baseline estimates of the growth trajectories (i.e., significant deviation from the control mean of zero). Significant declines (mean latent slope) in ECAS Total score and ALS Specific functions were found. ALS Non-Specific functions declined over time but did not reach statistical significance; however, a significant slope-intercept covariance was observed suggesting that higher baseline performance is related to slower decline.

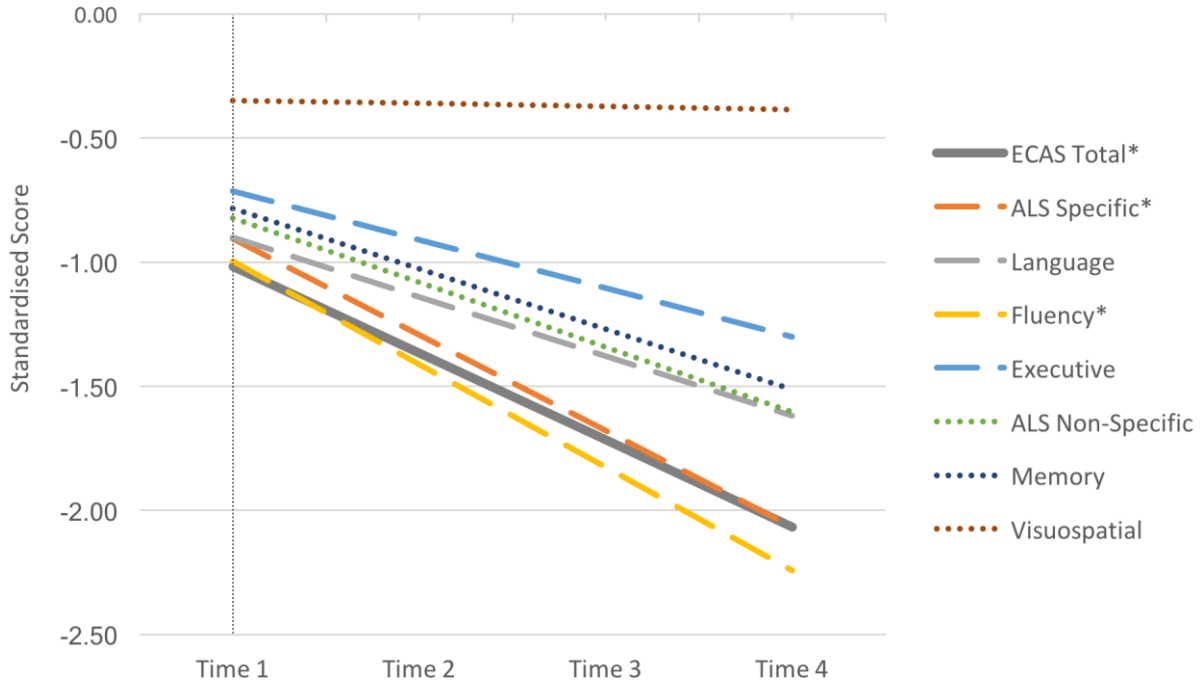
Regarding the ECAS cognitive subdomains, significant latent intercepts were found for verbal fluency, executive functioning, memory, and visuospatial domains. Conversely, only verbal fluency possessed a significant latent slope term. Significant intercept-slope covariance was found for memory functions. Figure 5.4 display the Basic LGCM model-implied trajectories for the ECAS cognitive domains.

Behaviour: For behavioural data, significant mean latent intercepts were observed for the behavioural score (i.e., number of behavioural domains present), and all individual behavioural domains indicating a significant deviation from zero for baseline functioning (see Table 5.6). However, none of the behavioural features possessed a mean significant slope, or slope-intercept covariance, demonstrating no significant change over time, and no relationship between baseline behaviour and change in probability over time.

As such, the ECAS Total, ALS Specific and fluency significantly declines over time once attrition has been included. ALS Non-Specific functions do not significantly decline over time, but are related to baseline performance such that

higher baseline performance is associated with a slower rate of decline. No change in the probability of behavioural features was observed over time.

Figure 5.4. Basic model-implied means for ECAS cognitive domains



Note. Graph represents model-implied means (z-scores) from LGCM controlling for attrition.

* = $p < .05$. Vertical line represents intercept of *y*-axis.

Table 5.6. Results of Latent Growth Curve Models for cognitive and behavioural functioning in ALS

	Basic LGCM			Covariate LGCM		
	Intercept	Slope	Cov *B*	Intercept	Slope	Cov
	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
ECAS Total	**-3.36 (1.09), *p* = .002**	**-1.68 (.716), *p* = .019**	.184 (.109), *p* = .091	-1.33 (1.55), *p* = .390	.101 (.906), *p* = .912	.095 (.077), *p* = .217
ALS Specific	**-3.45 (1.02), *p* = .001**	**-1.83 (.921), *p* = .048**	.117 (.121), *p* = .332	-1.68 (1.42), *p* = .238	1.04 (1.13), *p* = .359	.052 (.086), *p* = .545
Language	-.266 (2.21), *p* = .904	-1.58 (1.01), *p* = .119	-	-.083 (3.14), *p* = .979	-.593 (1.42), *p* = .677	-
Fluency	**-3.01 (1.32), *p* = .023**	**-2.64 (1.24), *p* = .033**	-.014 (.237), *p* = .954	-1.77 (1.77), *p* = .319	.578 (1.59), *p* = .716	-.148 (.240), *p* = .538
Executive	**-3.23 (.819), *p* < .001**	-.420 (.960), *p* = .662	.032 (.100), *p* = .750	-.901 (1.23), *p* = .465	1.23 (1.22), *p* = .313	.032 (.083), *p* = .702
ALS Non-Specific	**-2.64 (1.18), *p* = .036**	-.782 (.894), *p* = .382	**.378 (.165), *p* = .005**	-.615 (1.64), *p* = .708	-1.90 (1.717, *p* = .104	**.343 (.103), *p* = .001**
Memory	**-2.34 (.912), *p* = .010**	-.664 (.874), *p* = .447	**.251 (.098), *p* = .011**	-.481 (1.36), *p* = .723	-1.83 (1.15), *p* = .111	**.251 (.089), *p* = .005**
Visuospatial	**-3.45 (1.07), *p* = .001**	1.08 (1.82), *p* = .554	-	-1.87 (1.83), *p* = .308	1.21 (2.34), *p* = .605	-
Behaviour score	**2.47 (.910), *p* = .007**	1.03 (1.57), *p* = .512	-	2.47 (1.32) *p* = .062	-.815 (1.29), *p* = .526	-
ALSbi	**2.03 (.292), *p* < .001**	-.220 (.328), *p* = .503	-	**2.15 (.424), *p* < .001**	-.690 (.418), *p* = .099	-
Disinhibition	**1.17 (.228), *p* < .001**	.295 (.291), *p* = .310	-	**1.31 (.317), *p* < .001**	-.266 (.376), *p* = .479	-
Apathy	**1.63 (.276), *p* < .001**	.229 (.346), *p* = .508	-	**1.78 (.420), *p* < .001**	-.260 (.456), *p* = .568	-
Sympathy/empathy	**1.39 (.274), *p* < .001**	.075 (.367), *p* = .839	-.017 (.018), *p* = .366	**1.53 (.435), *p* < .001**	-.307 (.464), *p* = .507	-.018 (.017), *p* = .300
Perseveration	**1.41 (.262), *p* < .001**	.006 (.308), *p* = .985	-	**1.65 (.405), *p* < .001**	-.331 (.410), *p* = .420	-
Hyperorality	**1.67 (.274), *p* < .001**	.275 (.333), *p* = .409	-.034 (.022), *p* = .117	**1.21 (.400), *p* = .003**	.228 (.418), *p* = .586	.020 (.012), *p* = .098

Note. Cov = covariance. Significant values presented in bold. *B* coefficients for behaviour are the probit probability.

5.3.6. Effect of covariates on longitudinal cognitive and behavioural change (Aim 3)

Aim 3: *Examine the effect of age of onset, years of education, the presence of C9orf72 repeat expansion, and King's Clinical Disease Stage on longitudinal cognitive and behavioural change.*

To examine the effect of age of onset, years of education, the presence of C9orf72 repeat expansion, and King's Clinical Disease Stage on longitudinal cognitive and behavioural change, LGCMs from Aim 2 were expanded. The addition of time-invariant (age at onset, years of education, C9orf72 status) and time-variant covariates (King's Clinical Disease Stage) resulted in the loss of a significant mean intercept for all cognitive domains (Table 5.6). The significant slopes for ECAS Total, ALS Specific, and verbal fluency also became non-significant. The intercept-slope covariance found for ALS Non-Specific and memory functions in the Basic LGCMs persisted once disease stage, age at onset, years of education, and C9orf72 status were modelled. The intercept for behaviour score was no longer significant once disease stage was added. No other changes in behaviour domain models were found. As such, variation in baseline performance and rate of decline in cognition is explained by the model covariates (age of onset, education, C9orf72, and disease stage).

Table 5.7. Time-Invariant Covariates for full model

	Latent Intercept			Latent Slope		
	Age Estimate (SE)	Education Estimate (SE)	C9orf72 Estimate (SE)	Age Estimate (SE)	Education Estimate (SE)	C9orf72 Estimate (SE)
ECAS Total	-.013 (.010). *p* = .201	**.107 (.033), *p* = .001**	**-2.10 (.516), *p* < .001**	-.004 (.003), *p* = .207	-.003 (.011), *p* = .757	**-.474 (.125), *p* < .001**
ALS Specific	-.011 (.010), *p* = .267	**.112 (.031), *p* < .001**	**-2.14 (.439), *p* < .001**	-.004 (.003), *p* = .183	-.020 (.012), *p* = .093	**-.513 (.120), *p* < .001**
Language	.006 (.017), *p* = .746	**.108 (.053), *p* = .039**	**-3.50 (.980), *p* < .001**	-.001 (.005), *p* = .890	.006 (.020), *p* = .748	.054 (.242), *p* = .823
Fluency	-.009 (.012), *p* = .422	.075 (.039), *p* = .056	-.980(.587), *p* = .095	**-.010 (.005), *p* = .047**	-.110 (.020), *p* = .582	-.288 (.272), *p* = .290
Executive	**-.019 (.009), *p* = .025**	**.110 (.028), *p* < .001**	**-1.65 (.457), *p* < .001**	-.001 (.004), *p* = .873	-.020 (.015), *p* = .193	**-.469 (.196), *p* = .017**
ALS Non-Specific	-.015 (.010), *p* = .132	.060 (.032), *p* = .061	-.274 (.656), *p* = .676	-.005 (.005), *p* = .268	-.032 (.020), *p* = .115	-.021 (.304), *p* = .944
Memory	-.017 (.009), *p* = .058	**.062 (.029), *p* = .032**	-.046 (.507), *p* = .928	-.004 (.005), *p* = .429	.018 (.020), *p* = .382	-.033 (.329), *p* = .920
Visuospatial	-.009 (.012), *p* = .422	.075 (.039), *p* = .056	-.980 (.587), *p* = .095	**-.010 (.005), *p* = .047**	-.011 (.020), *p* = .582	-.288 (.272), *p* = .290
Behaviour Score	-.013 (.009). *p* = .171	**-.102 (.031), *p* = .001**	**1.04 (.448), *p* = .021**	-.001 (.005), *p* = .885	**.047 (.020), *p* = .020**	**.657 (.257), *p* = .011**
ALSbi	**-.008 (.003). *p* = .013**	-.020 (.010), *p* = .054	**.448 (.152), *p* = .003**	< .001 (.002), *p* = .802	**.014 (.006), *p* = .034**	**.156 (.078), *p* = .045**
Disinhibition	**-.008 (.002). *p* = .001**	-.009 (.008), *p* = .258	**.506 (.109), *p* < .001**	.002 (.001), *p* = .115	.004 (.006), *p* = .462	-.058 (.098), *p* = .554
Apathy	-.005 (.003). *p* = .110	-.014 (.010), *p* = .174	.229 (.160), *p* = .152	-.001 (.002), *p* = .453	.013 (.007), *p* = .062	**.260 (.088), *p* = .003**
Empathy	-.003 (.003). *p* = .370	**-.027 (.010), *p* = .011**	.029 (.144), *p* = .843	-.001 (.002), *p* = .421	**.023 (.007), *p* = .001**	**.288 (.086), *p* = .001**
Perseveration	-.002 (.003). *p* = .592	**-.030 (.010), *p* = .003**	.168 (.143), *p* = .238	.001 (.002), *p* = .629	.001 (.007), *p* = .939	.153 (.086), *p* = .076
Hyperorality	.004 (.003). *p* = .201	**-.029 (.010), *p* = .003**	**.285 (.137), *p* = .038**	-.002 (.002), *p* = .309	**.016 (.006), *p* = .009**	-.056 (.078), *p* = .477

Note. Significant values presented in bold. Age = age at onset, education = years of education, C9orf72 = positive or negative for repeat expansion.

5.3.6.1. Effect of age at onset, education, and genetic status (Aim 3)

The impact of age of onset, education, and genetic status are presented in Table 5.7. Age at onset had a limited effect on cognition, only significantly predicting baseline executive functioning, the rate of change for verbal fluency, and visuospatial functions. Education was a significant predictor of baseline performance of ECAS Total, ALS Specific, language, executive functioning, and memory but not on the rate of change. Conversely, C9orf72 status had a significant effect on the baseline performance for ECAS Total, ALS Specific, language, and executive functioning and significantly predicted the slope of ECAS Total, ALS Specific, and executive performance. As such, the presence of the C9orf72 repeat expansion significantly related to lower baseline cognitive and behavioural functioning and a faster rate of decline, while lower education related to lower baseline functioning but a faster rate of decline.

Age at onset significantly predicted the intercept for ALSbi and disinhibition, with education significantly predicting the intercepts of behavioural score, loss of sympathy/empathy, perseveration, and hyperorality. C9orf72 status predicted the intercept of behaviour score, ALSbi, disinhibition, and hyperorality. Regarding slope, age at onset had no effect on rate of change for any behavioural variable. Education predicted the rate of change of behavioural score, ALSbi, sympathy/empathy, and hyperorality. Conversely, genetic status predicted the slope of behaviour score, ALSbi, apathy, and loss of sympathy/empathy. Thus, fewer years of education and the presence of the C9orf72 expansion is associated with increased probability of behaviour features.

Table 5.8. Time-variant regression coefficients for ECAS domains on disease stage

	Time 1 Estimate (SE)	Time 2 Estimate (SE)	Time 3 Estimate (SE)	Time 4 Estimate (SE)
ECAS Total	-.072 (.065), *p* = .272	**-.155 (.069), *p* = .026**	**-.186 (.085), *p* = .029**	-.175 (.101), *p* = .083
ALS Specific	-.098 (.067), *p* = .144	**-.216 (.076), *p* = .005**	-.132 (.084), *p* = .117	-.097 (.106), *p* = .378
Language	.157 (.107), *p* = .142	.065 (.094), *p* = .490	.046 (.111), *p* = .678	.136 (.150), *p* = .362
Fluency	-.143 (.102), *p* = .159	**-.242 (.108), *p* = .025**	-.159 (.124), *p* = .202	-.054 (.164), *p* = .741
Executive	-.127 (.072), *p* = .079	**-.204 (.080), *p* = .010**	-.136 (.097), *p* = .158	-.218 (.129), *p* = .092
ALS Non-Specific	-.047 (.075), *p* = .530	-.088 (.082), *p* = .262	**-.350 (.118), *p* = .003**	**-.521 (.154), *p* = .001**
Memory	-.076 (.072), *p* = .293	-.093 (.081), *p* = .249	**-.291 (.116), *p* = .012**	**-.514 (.158), *p* = .001**
Visuospatial	.010 (.124), *p* = .934	-.151 (.081), *p* = .061	**-.488 (.137), *p* < .001**	**-.651 (.207), *p* = .002**
Behaviour Score	**.343 (.083), *p* < .001**	**.290 (.086), *p* = .001**	**.296 (.116), *p* = .011**	.222 (.174), *p* = .202
ALSbi	**.121 (.028), *p* < .001**	**.069 (.028), *p* = .014**	.048 (.038), *p* = .200	-.045 (.054), *p* = .409
Disinhibition	**.055 (.021), *p* = .010**	**.061 (.022), *p* = .006**	.060 (.032), *p* = .061	.006 (.047), *p* = .897
Apathy	**.107 (.028), *p* < .001**	**.079 (.028), *p* = .005**	**.082 (.039), *p* = .038**	.006 (.059), *p* = .925
Sympathy/empathy	**.099 (.029), *p* = .001**	**.066 (.027), *p* = .014**	.062 (.035), *p* = .073	.067 (.053), *p* = .204
Perseveration	.028 (.027), *p* = .303	**.056 (.026), *p* = .033**	**.098 (.037), *p* = .007**	**.123 (.055), *p* = .027**
Hyperorality	**.066 (.026), *p* = .013**	.036 (.023), *p* = .115	.004 (.028), *p* = .898	.005 (.046), *p* = .907

Note. Significant values presented in bold. B coefficients are the probit probability

5.3.6.2. Effect of disease stage (Aim 3)

Disease stage had a significant impact on cognition and behaviour at each time point (see Table 5.8). A separation was observed between ALS Specific and ALS Non-Specific functions, such that, disease stage significantly predicted ALS Specific cognitive functions in Time 2, whereas ALS Non-Specific functions were significant in Times 3 and 4. Specifically, disease stage was significant at Time 2 for ALS Specific, fluency, and executive functions. ALS Non-Specific, memory, and visuospatial functions were significantly related to disease stage at Times 3 and 4. ECAS Total, representing the combination of ALS Specific and Non-Specific, was significant for Times 2 and 3. The lack of significant effects of disease stage at Time 1 is due to the fact that time-invariant covariates (age of onset, education, and C9orf72) significantly predicted the latent intercept and therefore captured a significant proportion of baseline variability.

Similarly, behavioural features significantly related to disease stage mostly in earlier time points. All domains were significant at Time 1 except for for perseveration, and at Time 2 except for hyperorality. By Time 3, only behaviour score, apathy, and perseveration were significant, with perseveration the only significant behaviour domain at Time 4. As such, time and disease stage interact, with behaviour and ALS Specific functions affected more quickly in later disease stages, while ALS Non-Specific decline more slowly with advancing disease stage.

5.3.7. Unexplained Variances: Heterogeneity of neuropsychological functioning

Significant heterogeneity was present in the cognitive and behavioural data that was not fully accounted for by the full latent growth curve models. Residual variances are presented in Table 5.9. Residual slope variance was constrained to zero for language, visuospatial, behaviour score, ALSbi, apathy, disinhibition, and perseveration. Of the variables for which the residual slope variance was not constrained, only ALS Non-Specific functions were marginally significant. As such, the rate of longitudinal change in ECAS Total, ALS Specific, fluency, executive, memory, loss of sympathy, and hyperorality did not significantly differ between participants suggesting a homogeneous trajectory of change for the majority of cognitive and behavioural domains.

Contrary to the residual slope, all cognitive and behavioural domains demonstrated significant residual variation around the intercept. The significant variation suggest that baseline levels of cognitive and behavioural functioning are heterogeneous. While covariates included in the models are significant (Table 5.7), substantial variance remains unexplained. In addition to the slope and intercept, heterogeneity continued to exist for cognitive and behavioural functioning within each time point. For Time 1 (baseline), all variables except for ALS Specific, verbal fluency, and hyperorality, demonstrated significant residual variance. All cognitive and behavioural variables exhibited significant residual heterogeneity in Times 2 and 3. Conversely, by Time 4, ECAS Total, ALS Specific, ALS Non-Specific, fluency, executive, memory, and sympathy/empathy contained no significant residual variance. As such, the model explained the largest proportion of variance in these Time 4 domains.

Table 5.9. Residual variances of Covariate LCGMs

	Time 1	Time 2	Time 3	Time 4	Intercept	Slope
	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
ECAS Total	.327 (.146), p = .025	.550 (.124), p < .001	.746 (.158), p < .001	**.125 (.177), p = .482**	1.59 (.297), p < .001	**< .001 (.032), p = .990**
ALS Specific	**.271 (.189), p = .152**	1.22 (.218), p < .001	.431 (.111), p < .001	**.132 (.165), p = .424**	1.31 (.278), p < .001	**.010 (.039), p = .803**
Language	1.24 (.315), p < .001	.482 (.137), p < .001	.493 (.137), p < .001	.777 (.256), p = .002	3.84 (.837), p < .001	-
Fluency	**.433 (.381), p = .256**	2.31 (.423), p < .001	.888 (.244), p < .001	**.252 (.331), p = .446**	2.18 (.424), p < .001	**.115 (.094), p = .219**
Executive	.491 (.199), p = .013	1.16 (.207), p < .001	.464 (.124), p < .001	**.161 (.172), p = .350**	.879 (.245), p < .001	**.044 (.043), p = .309**
ALS Non-Specific	.685 (.241), p = .005	.485 (.134), p < .001	1.04 (.217), p < .001	**.136 (.238), p = .570**	1.30 (.352), p < .001	.115 (.058), p = .048
Memory	.640 (.184), p = .001	.484 (.119), p < .001	.659 (.176), p < .001	**.357 (.240), p = .137**	.999 (.250), p < .001	**.109 (.057), p = .056**
Visuospatial	3.80 (.464), p < .001	1.13 (.168), p < .001	3.60 (.627), p < .001	3.19 (.708), p < .001	-	-
Behaviour Score	.676 (.162), p < .001	.853 (.180), p < .001	.703 (.191), p < .001	.960 (.361), p = .008	.907 (.190), p < .001	-
ALSbi	.076 (.016), p < .001	.094 (.019), p < .001	.086 (.021), p < .001	.067 (.027), p = .014	.094 (.020), p < .001	-
Apathy	.091 (.020), p < .001	.107 (.021), p < .001	.084 (.022), p < .001	.093 (.036), p = .010	.073 (.019), p < .001	-
Disinhibition	.059 (.012), p < .001	.076 (.015), p < .001	.093 (.022), p < .001	.042 (.020), p = .038	.033 (.010), p = .001	-
Sympathy	.085 (.032), p < .001	.123 (.024), p < .001	.104 (.028), p < .001	**.094 (.056), p = .092**	.092 (.033), p = .005	**.003 (.011), p = .797**
Perseveration	.091 (.017), p < .001	.069 (.016), p < .001	.089 (.022), p < .001	.101 (.036), p = .005	.081 (.016), p < .001	**-**
Hyperorality	**.056 (.033), p = .091**	.102 (.019), p < .001	.070 (.017), p < .001	.138 (.050), p = .006	.092 (.034), p = .007	**.008 (.011), p = .470**

Note. Non-significant values *p*resented in bold

5.3.8. Latent Growth Curve Model Summaries

With regard to Aim 2, ECAS Total, ALS Specific, and fluency performance is found to significantly decline over time when attrition is controlled for. The significant decline in cognitive functioning over time is explained by advancing disease stage, the presence of the C9orf72 repeat expansion, and to a lesser degree age of onset (Aim 3). Time and disease stage have an interactive impact on cognitive functioning, such that differences in ALS Specific cognitive performance across disease stages appear quickly, while differences in ALS Non-Specific functions take longer to becomes apparent. The probability of behavioural features being present does not rely on time, but rather become more likely overall with fewer years of education, the presence of C9orf72 expansion, and advancing disease stage, with differences appearing quickly. Thus, ALS Specific and Non-Specific functions progress at different rates with disease progression. Lower baseline performance in ALS Specific functions is explained by fewer years of education, an older age of onset, and the presence of the C9orf72 mutation, with the C9orf72 mutation also contributing to a faster rate of decline. Lower baseline performance in ALS Non-Specific functions is related to fewer years of education, while the longitudinal trajectory is related to baseline levels i.e., better performance at baseline results in slower progression. A summary of the significant effects of the covariates are presented in Table 5.10 and 5.11.

Table 5.10. Summary of time-invariant associations for ECAS domains

	Predictors of baseline performance			*Predictors of rate of change*		
	Age	Education	C9orf72	Age	Education	C9orf72
Cognition						
ECAS Total	-	✓	✓	-	-	✓
Specific	-	✓	✓	-	-	✓
Language	-	✓	✓	-	-	-
Fluency	-	-	-	✓	-	-
Executive	✓	✓	✓	-	-	✓
Non-Specific	-	-	-	-	-	-
Memory	-	✓	-	-	-	-
Visuospatial	-	-	-	✓	-	-
Behaviour						
Behaviour Score	-	✓	✓	-	✓	✓
ALSbi	✓	-	✓	-	✓	✓
Disinhibition	✓	-	✓	-	-	-
Apathy	-	-	-	-	-	✓
Empathy Loss	-	✓	-	-	✓	✓
Perseveration	-	✓	-	-	-	-
Hyperorality	-	✓	✓	-	✓	-

✓ = significant relationship; - = non-significant relationship

Table 5.11. Summary of disease stage associations for ECAS domains

	Time 1	Time 2	Time 3	Time 4
		Cognition		
ECAS Total	-	✓	✓	-
Specific	-	✓	-	-
Language	-	-	-	-
Fluency	-	✓	-	-
Executive	-	✓	-	-
Non-Specific	-	-	✓	✓
Memory	-	-	✓	✓
Visuospatial	-	-	✓	✓
		Behaviour		
Behaviour Score	✓	✓	✓	-
ALSbi	✓	✓	-	-
Disinhibition	✓	✓	-	-
Apathy	✓	✓	✓	-
Empathy Loss	✓	✓	-	-
Perseveration	-	✓	✓	✓
Hyperorality	✓	-	-	-

✓ = significant relationship; - = non-significant relationship

5.3.9. Direct effect of disease stage on cognitive and behavioural functioning (Aim 4)

Aim 4: *Longitudinally verify the cross-sectional relationship between cognition, behaviour and disease stage presented in Chapter 4*

5.3.9.1. Raw Data

Data was restructured by disease stage, z-scores for which are presented in Table 5.12. The trend of cognitive performance across disease stage follows the same pattern as presented cross-sectionally in Chapter 4. Mixed effects models were conducted on the ECAS, ALS Specific, ALS Non-Specific, and behaviour domains, specifying a random intercept. Disease stage was treated as a fixed effect due to the lack of significant variation around the slopes of the latent growth curve models.

The addition of disease stage was significant against the baseline ECAS Total model ($\chi^2(3) = 14.50$, $p = .002$), with a significant linear polynomial ($t(110.42) = -3.25$, $p = .002$). A similar finding was observed for ALS Specific model ($\chi^2(3) = 13.02$, $p = .004$) with a linear polynomial ($t(133.68) = -3.23$, $p = .002$). The addition of disease stage for ALS Non-Specific was marginally significant over the baseline model ($\chi^2(3) = 7.95$, $p = .047$), with a quadratic polynomial trend ($t(101.06) = -2.01$, $p = .047$). All models were transformed to meet residual normality assumptions. The behavioural features model was significant ($\chi^2(3) = 27.83$, $p < .001$) with a significant linear polynomial ($t(140.03) = 4.45$, $p < .001$). Polynomials for ECAS Total ($p = .005$), ALS Specific ($p = .005$), ALS Non-Specific ($p = .047$), and behaviour ($p < .001$) survived correction for

multiple comparisons. None of the individual ECAS cognitive domains reached statistical significance.

Table 5.12. Cognition and behaviour by King's Clinical Disease Stage

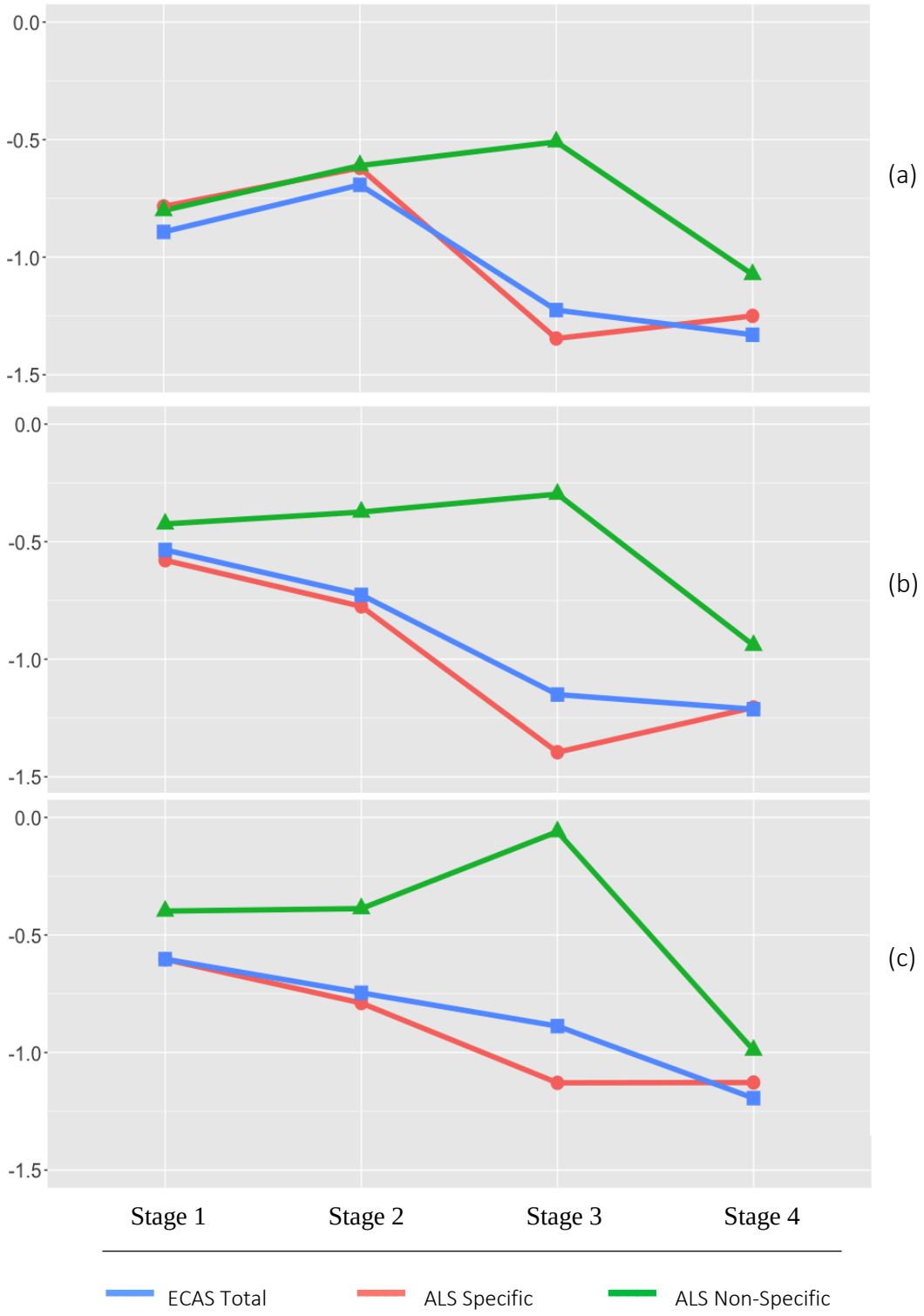
	Stage 1 (*n* = 40)	Stage 2 (*n* = 55)	Stage 3 (*n* = 37)	Time 4 (*n* = 87)
ECAS Total	-.89 ± 1.98*	-.69 ± 1.33	-1.22 ± 1.82*	-1.33 ± 1.87
ALS Specific	-.78 ± 1.71*	-.62 ± 1.35	-1.35 ± 2.05*	-1.25 ± 1.76
Language†	-.13 ± 1.02*	-.08 ± .960	-.50 ± 1.58	-.21 ± 1.03
Fluency	-.70 ± 1.53	-.42 ± 1.24	-1.43 ± 2.47	-1.43 ± 2.18
Executive	-.65 ± 1.40	-.48 ± 1.27	-.99 ± 1.64*	-.97 ± 1.56
ALS Non-Specific	-.80 ± 2.03	-.61 ± 1.28	-.51 ± 1.09	-1.07 ± 1.82
Memory	-.66 ± 1.51	-.63 ± 1.27	-.51 ± 1.04	-1.04 ± 1.71
Visuospatial†	.29 ± .390	.29 ± .390	.29 ± .440	.13 ± .630
	Stage 1 (*n* = 35)	Stage 2 (*n* = 50)	Stage 3 (*n* = 37)	Time 4 (*n* = 83)
Behaviour Score†	0 ± 0	0 ± 0	.67 ± .99	2 ± 1.48
Apathy	25.7	20.0	29.7	57.8
Disinhibition	11.4	10.0	16.2	33.7
Sympathy	17.1	30.0	24.3	48.2
Perseveration	22.9	18.0	27.0	41.0
Hyperorality	17.1	18.0	24.3	38.6
Psychosis	2.9	2.0	0.0	13.3

Note. Cognitive data is standardised z-score ± standard deviation; behavioural domains are percentages. * = one missing data point (i.e., *n* - 1). † = median and median absolute deviation presented.

Figure 5.5 displays the pattern of change for the ECAS composite cognitive domains, demonstrating a decline in ECAS Total, driven by ALS Specific functions, from Stage 2. ALS Non-Specific functions, similar to cross-sectional data, declined from Stage 3. To examine whether this pattern is driven

by Time 1 data (Chapter 4), data was also plotted with Time 1 data removed, and without patients who did not advance through disease stages over the course of the study. Overall, the removal of Time 1 data or patients who did not progress had no large impact on the pattern of decline. The separation of ALS Specific and ALS Non-Specific functions at Stage 3 persisted. As such, the cross-sectional findings reported in Chapter 4 are verified longitudinally.

Figure 5.5. Cognitive functioning by disease stage



Note. (a) All ALS patients' data (*N* = 161); (b) Data from Times 2, 3, and 4 (no Time 1; *n* = 101); (c) Data from patients who progressed to more advanced disease stages over the course of the study (*n* = 54).

5.3.9.2. Rates of impairment

Rates of impairment for ECAS cognitive and behavioural domains are presented in Table 5.13. Cochran-Mantel-Haenszel χ^2 test for count data was conducted on the ECAS Composite domains (ECAS Total, ALS Specific, ALS Non-Specific, and ALSbi). A significant effect was observed across disease stages for increasing rates of impairment (χ^2_{MH} (3) = 20.14, $p < .001$). Post-hoc Cochran-Armitage tests revealed that rates of ALS Specific impairment marginally related to advancing disease stage ($z = 1.69$, $p = .046$). However, this did not survive correction for multiple comparisons. Rates of ALSbi were significant after correction ($z = 4.14$, $p < .001$).

Table 5.13. Rates of impairment by King's Clinical Disease Stage

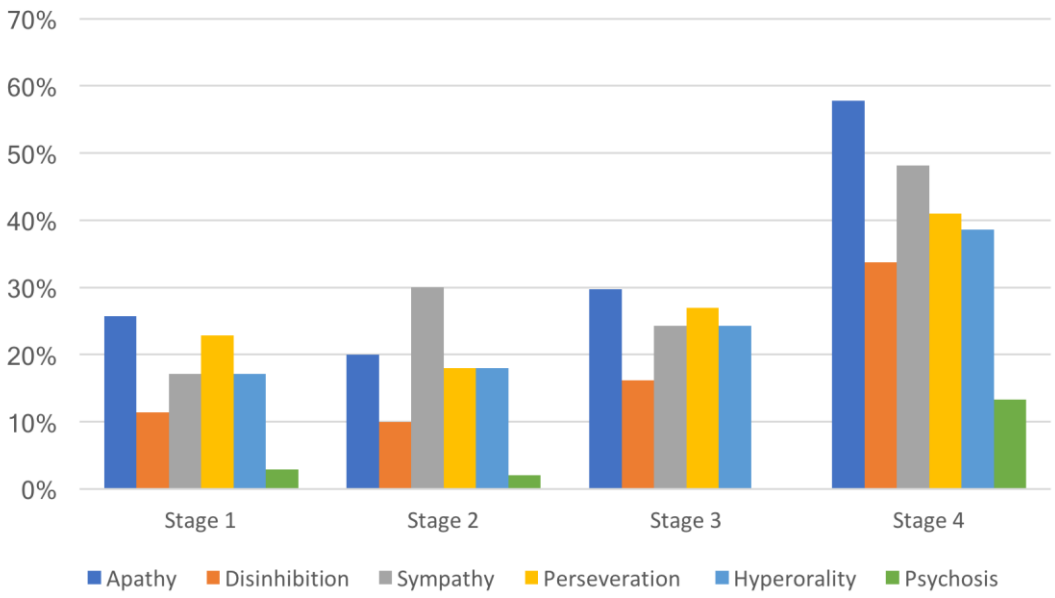
	Stage 1	Stage 2	Stage 3	Stage 4
ECAS Total	17.9 (*n* = 39)	18.2 (*n* = 55)	28.6 (*n* = 35)	27.9 (*n* = 86)
ALS Specific	15.4 (*n* = 39)	18.2 (*n* = 55)	34.3 (*n* = 35)	26.7 (*n* = 86)
Language	21.1 (*n* = 38)	32.7 (*n* = 55)	36.1 (*n* = 36)	29.1 (*n* = 86)
Fluency	15.0 (*n* = 40)	20.0 (*n* = 55)	25.0 (*n* = 36)	31.4 (*n* = 86)
Executive	15.0 (*n* = 40)	9.1 (*n* = 55)	28.6 (*n* = 35)	20.9 (*n* = 86)
ALS Non-Specific	18.0 (*n* = 39)	9.1 (*n* = 55)	5.6 (*n* = 36)	18.6 (*n* = 86)
Memory	17.5 (*n* = 40)	9.1 (*n* = 55)	2.7 (*n* = 37)	17.4 (*n* = 86)
Visuospatial	12.8 (*n* = 39)	3.6 (*n* = 55)	2.8 (*n* = 36)	15.1 (*n* = 86)
ALSbi	28.6 (*n* = 35)	30.0 (*n* = 50)	40.5 (*n* = 37)	62.7 (*n* = 83)
Impaired	42.4 (*n* = 33)	46.0 (*n* = 50)	48.6 (*n* = 35)	72.0 (*n* = 82)
Unimpaired	57.6 (*n* = 33)	54.0 (*n* = 50)	51.4 (*n* = 35)	28.1 (*n* = 82)

Note. Data is percentage. *N* = total sample for each cell. ALSbi classified as per Strong (2017) consensus guidelines. Impaired = presence of ECAS Total, ALS Specific, ALS Non-Specific impairment, or ALSbi. Unimpaired = absence of ECAS Total, ALS Specific, ALS Non-Specific impairment, or ALSbi.

Patients were classified as impaired if they possessed an impairment in the ECAS Total, ALS Specific, ALS Non-Specific, or behaviour domains. All other patients were considered unimpaired. Only patients with complete data for each domain were included. At Stage 1, 42.4% (n = 14) had a neuropsychological impairment, with 46% (n = 23) at Stage 2, 48.6% (n = 17) at Stage 3, and 72% (n = 59) at Stage 4.

Cochran-Mantel-Haenszel χ^2 tests were conducted on the cognitive subdomains (language, fluency, executive, memory, and visuospatial functions). A marginally significant effect was observed across disease stages for increasing rates of impairment (χ^2_{MH} (3) = 8.20, p = .042). Post-hoc Cochran-Armitage tests revealed that rates of fluency impairment significantly related to advancing disease stage (z = 2.18, p = .015), however this did not survive correction for multiple comparisons. No other cognitive domain was individually significant. Cochran-Mantel-Haenszel test for behavioural domains (apathy, disinhibition, loss of sympathy/empathy, perseveration, hyperorality, and psychosis) was significant across disease stages (χ^2_{MH} (3) = 74.57, p < .001). Post-hoc Cochran-Armitage tests corrected for multiple comparisons demonstrate that apathy (z = 4.30, p < .001), disinhibition (z = 3.43, p = .002), loss of sympathy/empathy (z = 3.31, p = .002), perseveration (z = 2.68, p = .007), hyperorality (z = 2.90, p = .006), and psychosis (z = 2.60, p = .007) significantly increase across disease stages (Figure 5.6).

Figure 5.6. Rates of behavioural features across King's Clinical Disease Stages



5.3.10. Relationship between rates of change in cognitive and behavioural domains (Aim 5)

Aim 5: *Examine how longitudinal changes in cognition and behaviour relate to one another*

Individual (random) model-implied slopes were extracted from the separate basic LGCMs to examine relationships among rates of change of ECAS subdomains. A Spearman correlation matrix of the relationship between the ECAS cognitive and behavioural domains is presented in Table 5.14, and displayed in Figure 5.7. The majority of slopes significantly correlated with each other, even after correcting for multiple comparisons. The strongest relationships were observed between language, fluency, apathy, and disinhibition. Interestingly, visuospatial functions related negatively with language, fluency, apathy, and disinhibition. This suggests a slower rate of visuospatial decline is related to a faster rate of decline

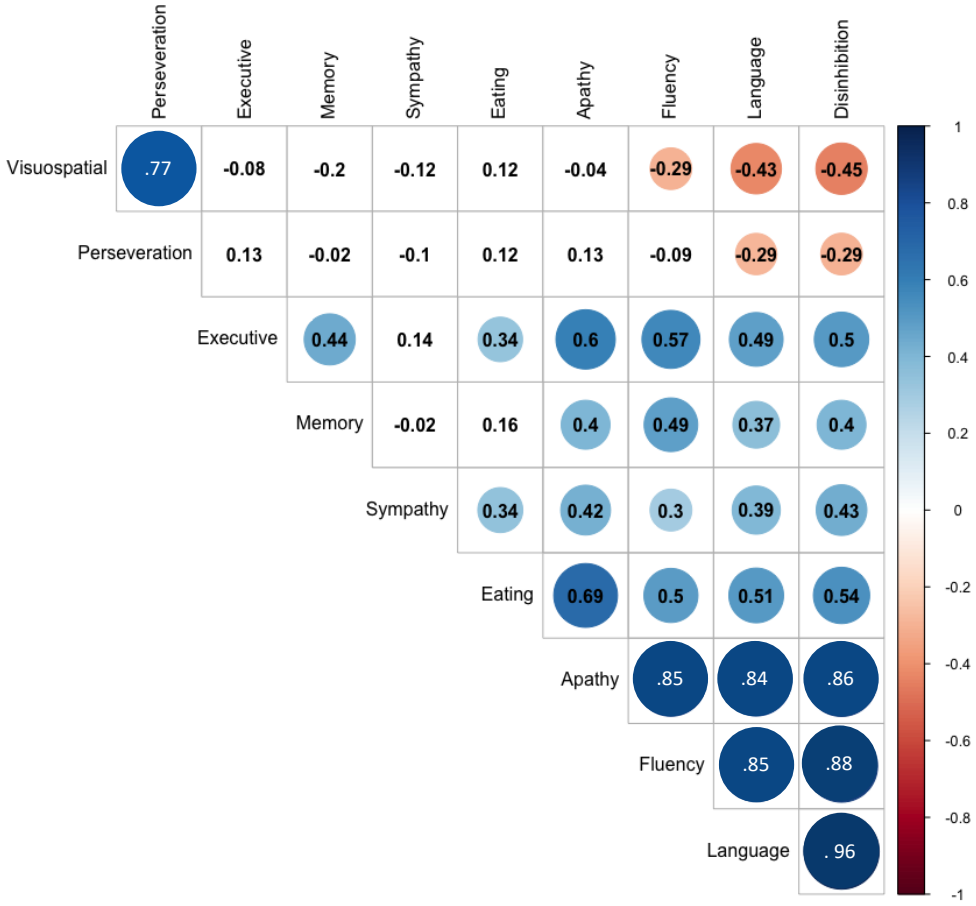
for language, fluency, apathy, and disinhibition. However, caution should be used in interpreting the model-implied values of visuospatial functioning, given the constraints placed on this model. The dendogram of clusters is presented in Figure 5.8. Of note, visuospatial functions and perseveration cluster together positively (*r* = .75), while executive functions and memory also form a cluster (*r* = .44). Fluency, language, apathy, and disinhibition form a single cluster, with fluency and apathy (r = .85), and language and disinhibition (.79) forming sub-clusters.

Table 5.14. Correlation matrix of model-implied slopes for the ECAS cognitive and behavioural Domains

	Language	Executive	Fluency	Memory	Visuospatial	Apathy	Disinhibition	Sympathy	Perseveration	Eating
Language		.49	.85	.37	-.43	.84	.96	.39	-.29	.51
Executive	< .001		.57	.44	-.08	.60	.50	.14	.13	.34
Fluency	< .001	< .001		.49	-.29	.85	.88	.30	-.09	.50
Memory	< .001	< .001	< .001		-.20	.40	.40	-.02	-.02	.16
Visuospatial	<. 001	> .999	.005	.306		-.04	-.45	-.12	.77	-.12
Apathy	< .001	< .001	< .001	< .001	> .999		.86	.42	.13	.69
Disinhibition	< .001	< .001	< .001	< .001	< .001	< .001		.43	-.29	.54
Sympathy	< .001	> .999	.005	> .999	> .999	< .001	< .001		-.10	.34
Perseveration	.006	> .999	> .999	> .999	< .001	> .999	.005	> .999		.12
Eating	< .001	.001	< .001	> .999	> .999	< .001	< .001	< .001	> .999	

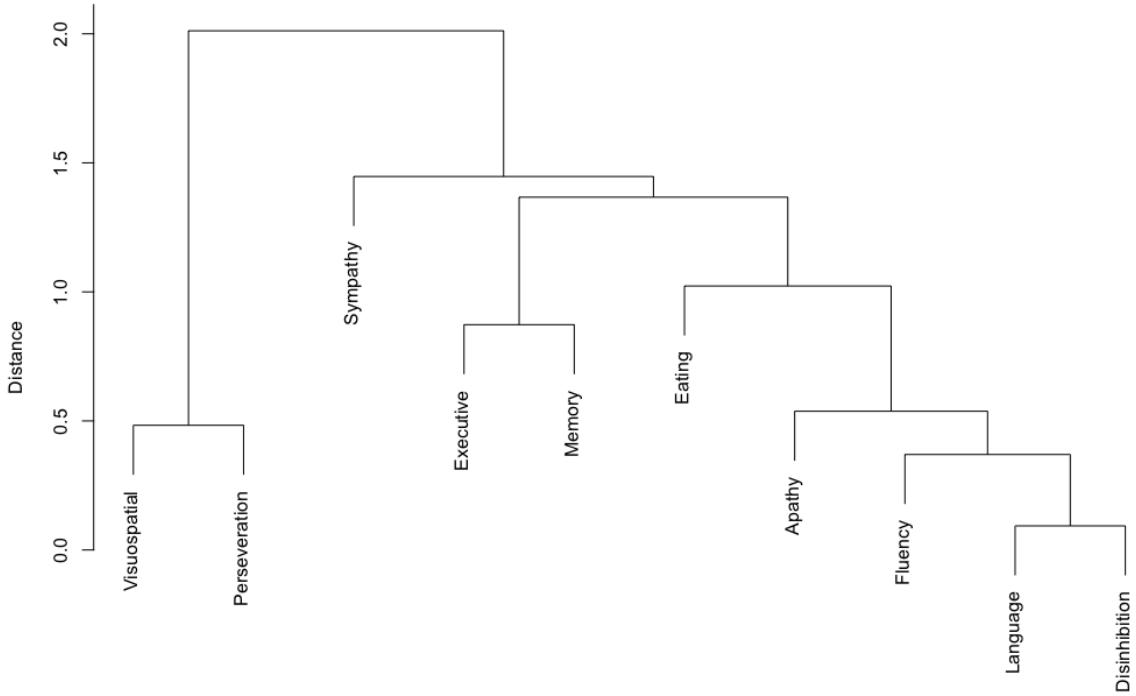
Note. Data in upper triangle is the Spearman correlation coefficient and data in lower triangle is the associated *p*-value. P-values Holm corrected for multiple comparisons.

Figure 5.7. Heatmap of model-implied slopes correlations for the ECAS cognitive and behavioural Domains



Note. Heatmap displays correlation coefficients (Spearman) for LGCM implied slopes, clustered by strength of relationship. Slopes for behavioural domains had their sign inverted (i.e., -multiplying slope by -1) to aid interpretation. Pairwise cells without colour circle are non-significant. Significance is Holm corrected as per Table 5.14.

Figure 5.8. Dendogram from hierarchical cluster analysis of LGCM slopes



5.3.11. Identification of patient subgroups (Aim 6)

Aim 6: *Evaluate the presence of ALS cognitive and behavioural subgroups*

Hierarchical cluster analysis was also conducted on individual patients' model-implied slopes to evaluate the presence of patient subgroups. The dendogram revealed a four-group solution (Group A: *n* = 67, Group B: *n* = 72, Group C: *n* = 20, and Group D: *n* = 2). Severe cognitive and behavioural impairments were observed in Group D patients. One patient's ECAS Total z-score at Time 1 was -6.12 which declined to -10.12 by Time 4. Conversely, their behaviour (4 behavioural features) and depression (HADS depression = 17) improved from Time 1 to Time 4 (two behavioural features and HADS depression score of 2).

This patient transitioned from Stage 2 to Stage 4 over the course of the study. The second patient was in Stage 1 but dropped-out after Time 1. An ECAS total z-score of -11.69, 5 behavioural features, and psychosis were observed. This patient was previously excluded as an outlier from the visuospatial model. Due to the small sample size, Group D was not analysed further.

The mean model-implied trajectories of patients' cognitive and behavioural functioning by group membership are displayed in Figure 5.9. Patients in Group A (40.4% of sample) demonstrate no decline in cognitive functioning and no increase in the probability of behavioural features. Groups B (44.1%) and C (14.3%) demonstrate a longitudinal model-implied decline in cognitive and behavioural functioning, with Group C showing a faster decline in memory functions, in addition to lower baseline performance in all domains except for visuospatial. As such, Groups A to C demonstrate a gradation of rates of decline.

Demographic and clinical variables were compared between patient subgroups, with significant results reported in Table 5.15. No demographic variables (years of education, gender, SES) significantly differed between groups. Clinical disease variables (age of onset, diagnostic delay, Riluzole use, ALSFRS-R, depression, anxiety, C9orf72 status, site of onset, and disease stage) were compared between groups. A gradation of older age of onset, lower ALSFRS-R score, and more advanced disease stage was observed across groups with faster rates of decline. For site of onset, Group A had fewer than expected bulbar onset patients and more than expected upper limb onset patients (standardized residuals of -1.8 and +1.8 respectively), while for Group B the inverse pattern was observed (+1.1 and -.85 respectively). Group C had fewer

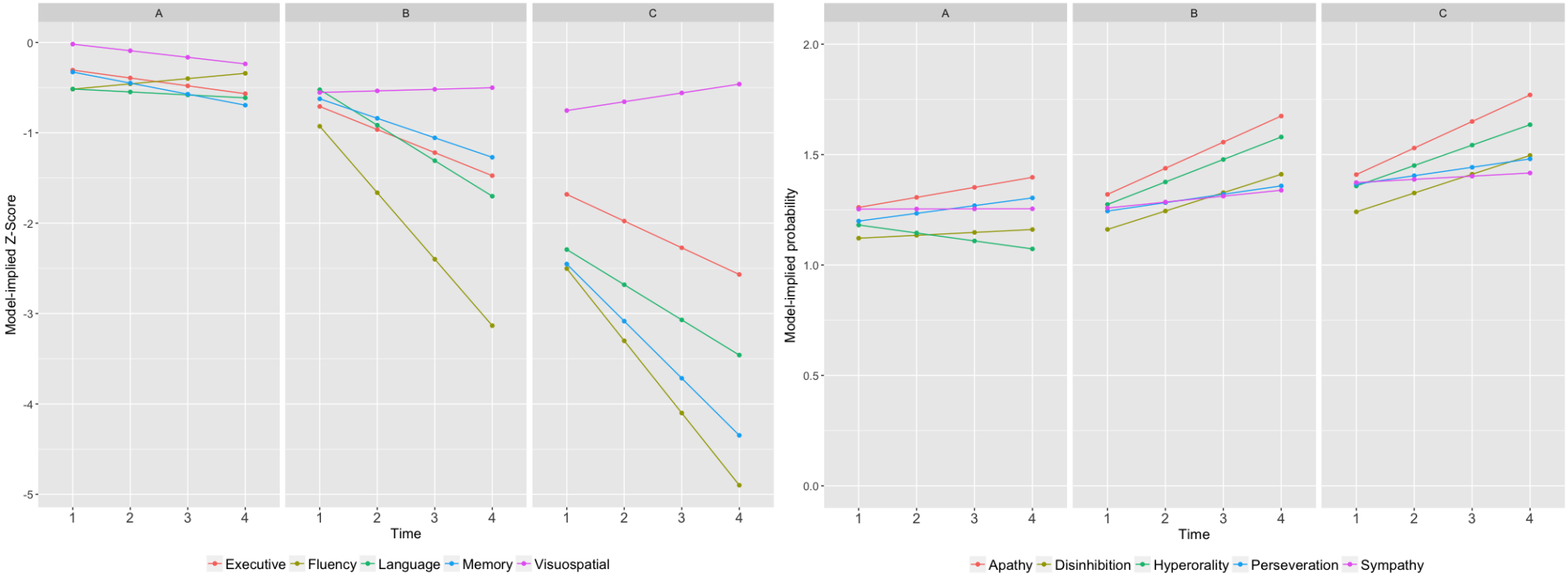
upper limb (-1.5) and a greater number of bulbar onset patients (+1.01). However, when results were corrected for multiple comparisons, none survived (all $p > .05$)

Table 5.15. Significant demographic and clinical comparisons of hierarchical clusters

	Group A *n* = 67	Group B *n* = 72	Group C *n* = 20	*F* or X^2	*p*
Age at onset	56.40 ± 12.92	61.53 ± 10.63	62.15 ± 9.91	3.70	.027
ALSFRS-R	39.95 ± 6.04	36.85 ± 7.77	37.20 ± 5.65	4.35	.015
Site of onset % (B/UL/LL/R/M)	13/39/33/2/13	33/25/36/1/4	35/10/40/0/15	11.68	.020
Disease Stage*	2 ± 1.48	2 ± 1.48	4 ± 0	6.89	.032

Note. B = Bulbar, UL = Upper Limb, LL = Lower Limb. For site of onset, only B, UL, and LL were analysed. * = median reported ± median absolute deviation. *P*-values not corrected for multiple comparisons. Disease stage analysed using Kruskal-Wallis test.

Figure 5.9. Cluster-based subgroups of model-implied means



Note. Subgroups were determined based on model-implied slopes. Graphs above represent the mean of each patients' model-implied scores for each time point.

5.4. Discussion

The aims of this chapter were to 1) examine the effect of neuropsychological impairment and disease stage/severity on attrition; 2) examine longitudinal changes in cognition and behaviour over time using appropriately specified models which control for attrition, 3) examine the effect of age of onset, years of education, the presence of C9orf72 repeat expansion, and King's Clinical Disease Stage on longitudinal cognitive and behavioural change; 4) Longitudinally verify the cross-sectional relationship between cognition, behaviour and disease stage presented in Chapter 4; 5) examine how longitudinal changes in cognition and behaviour relate to one another; and 6) evaluate the presence of ALS cognitive and behavioural subgroups.

Cognitive functioning was found to significantly decline over time, particularly the ECAS Total, ALS Specific, and verbal fluency scores. This is in contrast to previous studies that did not control for attrition, which may have masked a decline. Furthermore, cognitive and behavioural impairment was found to significantly predict attrition, highlighting its importance in longitudinal analysis. The effect of time was attenuated when covariates of interest (age of onset, years of education, C9orf72 status, and King's Clinical Disease Stage) were modelled suggesting that longitudinal changes were dependent on these covariates. No significant decline in behavioural functioning was found (i.e., an increase in probit probability), however, behaviour was found to be related to disease stage in addition to the presence of C9orf72 mutation and education. ALS Non-Specific functions and memory did not demonstrate a significant decline over time, but the

rate of change was related to baseline performance such that higher baseline performance resulted in a slower rate of decline.

When data was restructured by disease stage, cognitive and behavioural functioning were found to decline in the same pattern as observed cross-sectionally (Chapter 4). In particular, ALS Specific functions declined from earlier disease stages whereas ALS Non-Specific functions were driven by end-stage disease. When rates of decline in different ECAS subdomains were examined, distinct but overlapping clusters were observed. Apathy, fluency, language, and disinhibition strongly correlated. Executive functions and memory formed its own related cluster, while visuospatial functions and perseveration formed a separate cluster. In analysing subgroups of patients, a four-group solution was observed with sequentially more severe cognitive and behaviour decline.

5.4.1. Longitudinal changes in cognition and behaviour

Previous longitudinal studies of cognition in ALS has produced inconsistent findings. Attrition has significantly challenged the appropriate modelling of longitudinal outcomes in ALS, with cognitive impairment linked with increased risk of attrition (Elamin et al., 2013), which was also found in the present study. It is demonstrable from the present findings that longitudinal studies of cognition and behaviour in ALS must account for non-random attrition in appropriately specified models. Mean scores displayed in Table 5.3 suggest an improvement over time. However, once attrition was controlled for, cognitive functions were found to decline. This point has important implications when previous longitudinal results are considered. It is likely that the inconsistency of previous research is, in part, due to biased statistical procedures.

Furthermore, previous research has suffered from the use of tests dependent on motor speed, the presence of practice effects, small sample sizes, limited follow-up occasions, high rates of attrition, and the lack of a control group. The present study included the ECAS (Abrahams et al., 2014) and its alternate forms (Crockford et al., 2017a; 2017b) which allowed for the measurement of cognition, independent of motor speed and robust to practice effects. The addition of a matched control group, allowed for the conversion of patient raw scores to standardised scores, further reducing the potential impact of practice effects. The present study included a large multicentre sample of 161 patients, measured over four time points, with acceptable rates of attrition improving the sensitivity to detect a longitudinal effect. Therefore, the present study addresses the methodological restrictions which limited the interpretation of previous reports.

Once attrition is accounted for, cognitive functioning was found to decline significantly over time. Different cognitive domains are affected by time in different ways. As displayed in Figure 5.4, the model-implied trajectories suggest that the rate of decline for ECAS Total, ALS Specific, and fluency differ from those of ALS Non-Specific, executive, memory, and language functions. All ECAS cognitive domains except for visuospatial functions demonstrate a mean model-implied decline over time, with ECAS Total, ALS Specific, and fluency declining at a faster rate and significantly. The significant intercept-slope covariance for ALS Non-Specific and memory functions suggests that higher baseline performance relates to a slower rate of change. Elamin et al. (2013) similarly observed that ALS patients with non-executive cognitive impairment (e.g., memory impairment) at baseline declined more quickly in memory functions compared to patients with a profile of executive impairment at baseline.

Executive functions, memory, and language declined over time but the trajectory of the latent slope was not significant. Of importance, however, is the significant decline in verbal fluency performance. Verbal fluency has been identified as the most sensitive marker of cognitive impairment in ALS. Recently updated consensus guidelines suggest that verbal fluency impairment alone is now sufficient to categorise ALS patients as cognitively impaired (Strong et al., 2017). In addition to the extensive work by Abrahams and colleagues (e.g., 2004), it has been observed that the majority of ALS patients with executive dysfunction have verbal fluency impairment (Phukan et al., 2012), and that when clinical neuropsychological tests are re-organised into functional domains, cognitive initiation is most common impairment (Kasper et al., 2015).

Despite a consistent positive trend for increasing probability, no significant changes in behaviour were observed over time. Yet, our previous cross-sectional findings (Crockford et al., 2018; Chapter 4) suggest that behaviour is significantly related to disease stage. It is possible that time may be a poor indicator of longitudinal behaviour changes. Alternatively, this may suggest that changes in behaviour are at a slower pace than changes in cognitive functioning, or may come secondary to cognitive decline.

5.4.2. Longitudinal neuropsychological functioning and disease stage

In Chapter 4 it was observed that disease stage is an important factor in cognitive and behavioural features of ALS. When covariates were added to LCGMs, the significant decline observed for ECAS Total, ALS Specific, and fluency functions is ameliorated suggesting that longitudinal decline in cognitive functioning is dependent on the covariates rather than time. Rate of change in ALS Non-

Specific functions remained dependent on baseline levels of functioning, even after the inclusion of covariates. ALS Specific functions and behaviour were found to significantly relate to disease stage in earlier time points, while ALS Non-Specific functions and perseveration are dependent on disease stage in later time points. The interactive relationship between disease stage, time, and cognitive domains demonstrate that ALS Specific and Non-Specific functions react differently to disease stage, as suggested cross-sectionally in Chapter 4.

In Chapter 4 it was shown that largest difference in disease stage for ALS Specific cognitive functions was from Stage 2 to Stage 3. ALS Non-Specific functions, conversely, differ the most between Stage 3 and 4. Longitudinally, patients in earlier disease stages were seen to transition to later disease stages, with the majority of patients in end-stage disease in Times 3 and 4. Given this, Times 1 and 2 are optimal to detect the effect of disease stage on ALS Specific functions as it provides greater coverage of Stages 1-3. Similarly, Times 3 and 4 are optimal to detect an effect of disease stage on ALS Non-Specific functions due to the greater coverage of Stages 3 and 4. As such, the estimate of disease stage within the LGCMs corroborate the cross-sectional findings in Chapter 4. Furthermore, the patterns of change observed in cognitive and behaviour functioning longitudinally supports the hypothesis presented in Chapter 4, that underlying disease pathology may explain the relationship between cognition, behaviour, and disease stage. Specifically, it has been proposed that disease spread in ALS follows a predictable pattern whereby TDP-43 inclusions beginning in the primary motor cortex, spinal cord, and cranial nerves, spreading to the reticular formation of the brainstem, the prefrontal cortex, and finally the hippocampus (Brettschneider et al., 2013). Based on this hypothesis, we would

expect to see deterioration in ALS Specific functions early in the disease course with ALS Non-Specific functions developing later, which was observed. There is no current research available on the neural correlates of the King's Clinical Disease Stage and therefore one cannot assume that disease stage necessarily reflects pathological disease spread. Rather, disease stage represents clinical disease progression which may or may not decline at a similar rate to pathological progression. As such, the time by stage by cognitive domain interaction seen in the present study may reflect the differences in clinical and pathological disease spread.

To further explore the relationship between disease stage and neuropsychological functioning, in addition to verifying the results of Chapter 4 longitudinally, data were restructured by disease stage rather than time. When disease stage is modelled directly, ECAS Total, ALS Specific functions, and behaviour features were significantly and linearly related to disease stage, while ALS Non-Specific functions possessed a marginally significant quadratic curve. Interestingly, none of the individual cognitive domains reached significance suggesting an aggregative effect. However, this may also be due to a lack of power to detect individual trajectories. When data are restructured by disease stage, a loss of information occurs such that the pairwise coverage of adjacent disease stages is reduced. Similar findings were observed for rates of impairment, such that a significant main effect for ECAS composite domains was observed. The cognitive subdomains did not reach statistical significance on post-hoc analysis, however, behavioural features (apathy, disinhibition, loss of sympathy, perseveration, hyperorality, and psychosis) did.

While it was observed that attrition is significantly predicted by neuropsychological impairment, it is not possible to control for attrition in the mixed effects analysis of disease stage, nor the analysis of impairment rates. Indeed, these findings are biased such that patients with more severe cognitive, behavioural, and physical features were less likely to continue taking part. Therefore, the rates of impairment observed longitudinally likely underestimate the true rates of impairment. We observed that neuropsychological impairment was present in 80% of Stage 4 patients cross-sectionally and 72% of patients longitudinally. Thus, longitudinal results largely corroborate findings of cross-sectional analyses (Chapter 4).

5.4.3. Longitudinal neuropsychological functioning and age of onset, years of education, and the C9orf72 mutation

Age of onset, years of education, and C9orf72 status have previously been associated with cognitive and behavioural impairment (e.g., Beeldman et al., 2016; Byrne et al., 2012; Elamin et al., 2011; & Trojsi et al., 2016). A small number of significant associations were found between age of onset and baseline executive functioning, behavioural impairment, and disinhibition, in addition to rate of visuospatial and fluency decline. The comparatively few significant relationships between age of onset and neuropsychological functioning suggests that cognitive decline in ALS is not entirely a product of age-related cognitive decline. Time-variant covariates were largely predictive of baseline behaviour and ALS Specific functions, particularly years of education and the presence of C9orf72 mutation. Years of education and C9orf72 was also related to the

increased probability of behavioural features. Conversely, the C9orf72 mutation, and not education, was associated with the rate of change in ALS Specific functions. Therefore, ALS specific functions and behaviour are dependent on disease stage, education, and the presence of C9orf72 repeat expansion. The relationship between covariates and the latent intercept explain the lack of significant associations between Time 1 data and disease stage, in that these covariates explain a significant proportion of baseline performance.

Cognitive reserve may be a factor in the effect of education, defined as "individual differences in how people process tasks allowing some to cope better than others with brain pathology" (Stern, 2009, *pp*. 2016). Cognitive reserve describes the lack of direct relationship between severity of pathology and degree of impairment (Stern, 2002; Scarmeas & Stern, 2003) and the use of compensation strategies, such that participants recruit intact brain structures to overcome pathological structures. For example, participants may recruit aspects of intact executive functioning to complete memory performance. Years of education has been shown to contribute to cognitive reserve (Kaplan et al., 2009) and significantly relate to lower incidence of dementia (Valenzuela & Sachdev, 2006). Montuschi et al. (2015) classified a cohort of ALS patients as ALS-FTD, ALS-NECI (non-executive cognitive impairment), ALS-ECI (executive cognitive impairment), ALS-Bi (behavioural impairment), and ALS-NCCI (non-classifiable cognitive impairment), and cognitively intact. The authors report that ALS-FTD patients had lower education compared to all other patient subgroups, suggestive of cognitive reserve. Cognitive reserve has been related to reduced metabolism in the dorsolateral prefrontal cortex (Dodich et al., 2018). However, education was not found to relate to the rate of change in cognitive functions. This may

suggest that the protective influence of cognitive reserve only has a non-significant effect

It is perhaps unexpected that years of education is related to behavioural functioning, yet, such a theory has previously been suggested. Premi et al., (2013) explored the concept of *behavioural reserve* in the context of FTD observing that FTD patients with higher education levels possessed a higher degree of frontotemporal hypoperfusion, despite similar disease severity and disinhibition scores. Behavioural changes in FTD have been associated with hypometablism in frontotemporal regions, including the anterior cingulate and temporal cortex, and the dorsolateral prefrontal cortex (Borroni et al., 2012). As such, educational attainment may be protective in trajectories of ALS behaviour, or allow for the use of compensation strategies.

The C9orf72 expansion accounts for up to 50% of familial cases and 8% of sporadic ALS cases (De Jesus-Hernandez et al., 2011; Hardiman et al., 2016; Majounie et al., 2012). Genetically, the presence of FTD in ALS has been associated with the C9orf72 expansion, seen in approximately 12% of familial FTD cases and 24% of familial ALS cases (Byrne et al., 2011; De Jesus-Hernandez et al., 2011). C9orf72 has been associated with higher rates of cognitive and behavioural impairment, dementia and neuropsychiatric features (Byrne et al., 2012; Hardiman et al., 2016; Snowden et al., 2013). Westeneng et al., (2016) found widespread cortical and subcortical grey matter differences between C9orf72 carriers and non-carriers, in addition to reduced white matter integrity of the inferior and superior longitudinal fasciculus. In the present study, C9orf72 carriers had worse baseline cognitive and behavioural functioning (ECAS Total, ALS Specific, language, executive, behaviour score, hyperorality),

in addition to faster rates of decline in the ECAS Total, ALS Specific, executive, behaviour score, apathy, and loss of sympathy/empathy. However, given the small number of patients identified as carriers, caution should be used in interpreting these results. Of the 38% of patients for whom genetic status was unavailable, it is highly likely that there exists C9orf72 carriers in this subsample. This likely contributes, in part, to the significant residual variation present in the latent variable models.

5.4.4. Relationship among individual ECAS domains

With regards to Aim 5, cognitive and behavioural subdomains formed distinct but related clusters. Executive functioning and memory formed a subgroup, related to the fluency, language, apathy, and disinhibition subgroup suggesting that these domains tend to decline at similar rates. The relationship between executive functioning and memory in ALS has been previously examined in the literature, with the suggestion that memory impairment observed in ALS may be partly explained by executive dysfunction (Christidi et al., 2012; Machts et al., 2014; Mantovan et al., 2003). Indeed, the hierarchical cluster analysis established a significant relationship between the rate of change for memory and executive functioning, demonstrating that the rate of change in memory relates to the rate of change in executive functions. This finding appears at odds with the observation that executive functions are affected at earlier disease stages than memory functions. However, the decline in executive functions begins in earlier stages and continue into end stage disease, converging with memory functions by Stage 4. Additionally, these correlations are based on random (individual) latent slopes, suggesting that at least a proportion of patients' executive and

memory functions co-vary. Thus, executive decline may be partially driving the decline in memory functions, or vice versa.

Verbal fluency, apathy, language, and disinhibition additionally group together. Verbal fluency has previously been associated with apathy, with the suggestion that this profile of neuropsychological impairment may represent a deficit in cognitive and behavioural initiation (e.g., Radakovic et al., 2017c). Our findings similarly suggest that the rate of decline in verbal fluency is strongly associated with an increased probability of apathy. In addition to the extensive work by Abrahams and colleagues (e.g., 2004), it has been observed that the majority of ALS patients with executive dysfunction have verbal fluency impairment (Phukan et al., 2011), and that when clinical neuropsychological tests are re-organised into functional domains, cognitive initiation is most common impairment (Kasper et al., 2015). In our analysis, verbal fluency and executive functions did not form a unique cluster, but did correlate strongly (r = .57).

Visuospatial functioning and perseveration formed a discrete group, correlating positively and strongly. Interestingly, visuospatial functions and perseveration were negatively related to domains of the first grouping (language, disinhibition, and fluency) suggesting separation. Visuospatial functions and perseveration also possessed unique properties in the LGCMs. While most cognitive domains demonstrated a decline in functioning over time (significant or non-significant), visuospatial functioning was the only domain to demonstrate a flat slope. Perseveration, instead, was the only behavioural domain to relate to disease stage in later time points. While visuospatial functions did not demonstrate a declining slope in the latent growth curve models, this does not indicate that no patient declined, but rather than the group mean was flat. As

such, patients who declined in visuospatial functions also had an increased probability of having perseverations, and similarly, those who demonstrated no change in visuospatial functions showed no change in the probability of perseveration. However, it should be noted that the models for visuospatial functions and perseveration possessed numerous constraints, suggesting instability in the LGCMs and caution should be used in interpreting these models' outputs.

5.4.5. Identification of model-implied patient subgroups

Individual patients were clustered into three groups (once two outliers were removed; Group D) characterised by progressively faster rates of longitudinal decline in neuropsychological functioning. A faster rate of decline was associated with a constellation of clinical and demographic features, namely older age of onset, lower ALSFRS-R scores, site of onset, and more advanced disease stage. The findings that age of onset, and disease stage significantly differ between groups supports their inclusion in covariate LGCMs. While these comparisons did not survive correction for multiple comparisons, they indicate that the rate of decline in neuropsychological functioning is complex and multicomponent, with no conspicuous contributing risk factors. However, the relationship with the ALSFRS-R and King's Clinical Disease Stage support the findings of the latent growth curve models that cognitive and behavioural functioning is related to disease progression. Yet, an important limitation to note is that these subgroups are theoretical in nature. The values utilised in establishing subgroups are inferred from the models, with missing data points estimated. Given the

relationship between neuropsychological impairment and attrition, Groups B and C with the fastest decline also contain patients more likely to drop-out.

5.4.6. Limitations and conclusions

The present study aimed to overcome limitations of previous longitudinal research in ALS, namely, small sample sizes, bias introduced by attrition, use of cognitive tests not appropriate for reduced motor speed, presence of practice effects, and the use of time as the only proxy of progression. Indeed, the methodological design of this study overcame many of the issue, yet some important limitations should be considered. The model fit in this study utilised linear slopes, i.e., that change over time follows a linear pattern. However, it is possible that a quadratic growth function would also be appropriate for such data. The present data unfortunately did not accept the quadratic slopes due to loss of fit and misspecification. The negative variances observed in language and visuospatial functions point to the lack of variability in performance between patients, which may be in part due to the ceiling effects present in the raw data. As such, the models with poorer fit or issues around specification should be interpreted with caution. For instance, the full covariate models for language, ALS Non-Specific, and disinhibition possess poor or acceptable fit. Additionally, visuospatial functions and all behaviour domains except loss of sympathy/empathy and hyperorality required model constrains. Additionally, given the impact that attrition has on the trajectory of changes, it was not possible to compute accurate group-level analyses of reliable change reported in Chapter 3.

In summary, significant ALS Specific cognitive and behavioural decline is apparent in patients with ALS, and is related to advancing clinical disease stage. Fewer years of education related to worse cognitive and behavioural functioning, and the presence of C9orf72 repeat expansion related to worse a faster rate of decline in ALS Specific cognitive and behavioural functioning. ALS Non-Specific functions are related to disease stage and age of onset at baseline, with the rate of change dependent on baseline performance. ALS Specific and Non-Specific interact with disease stage and time in their progression profiles, such that ALS Specific functions (in addition to behaviour) decline more quickly than ALS Non-Specific functions.

The observations from Chapters 4 and 5 indicate that cognition and behaviour decline over the ALS disease course and are critically related to disease stage. Given the prominent impact that neuropsychological impairment on burden, quality of life, survival, and medical care, and the suggestion that all patients with ALS should undergo neuropsychological screening (e.g., NICE, 2016; Strong et al., 2017), the question arises as to the practices of clinicians caring for people with ALS. The following chapter will examine clinicians' attitudes and barriers to cognitive and behavioural screening.

CHAPTER 6: Clinicians' attitudes toward cognitive and behavioural screening in motor neurone disease

In Chapters 2-3, the development of alternate forms of the ECAS was described to allow for repeated assessment of cognition in ALS. Chapters 4-5 describe the application of these new ECAS forms in describing cognition and behaviour across King's Clinical Disease Stages. It was observed that ALS-Specific cognitive changes and behaviour was critically associated with advancing disease stage. Given the prevalence of cognitive and behavioural impairment in ALS, and the findings herein that cognitive functioning declines over the course of the disease, it is important to understand how neuropsychological assessment and clinicians interact.

Chapter 6 describes a qualitative investigation of clinician's attitudes toward neuropsychological assessment in ALS and the barriers to such assessment. The following chapter, in its current form, was accepted for publication in the *British Journal of Neuroscience Nursing* (DOI: https://doi.org/10.12968/bjnn.2017.13.3.116). Chapter 6 was not published open-access, and therefore represents the pre-proof version of the manuscript.

Note: The interview script associated with this chapter is available in Appendix VI'.

Title: Clinicians' attitudes toward cognitive and behavioural screening in motor neurone disease

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6.1. Abstract

Amyotrophic Lateral Sclerosis (ALS), the most common variant of Motor Neurone Disease, is a fatal neurodegenerative condition marked by progressive motor disability. Cognitive and behavioural changes occur in approximately 50% of patients, which may impact caregiver burden, adherence to life-prolonging interventions, and care planning. The aim of this study was to explore the attitudes and practices of Health Care Professionals working with ALS patients in Scotland towards cognitive and behavioural screening. Structured interviews with ALS Healthcare Professionals were conducted and subjected to thematic analysis. While 93% of clinicians in this study believed that cognitive and behavioural screening should be routinely applied for all patients, it is not currently common practice, nor are formalised screening tools widely used. Participants noted that barriers to screening include other members of staff, limited resources, and issues concerning patients and their families. Participants suggested that increased education and training, making screening a standardised protocol to all patients and increased psychology input may help overcome these barriers.

Key points:

1. Cognitive and behavioural screening in MND is important in the management and care of patients and their families, as highlighted by recently updated guidelines from the National Institute for Health and Care Excellence (NICE).

2. While the majority of Health Care Professionals in this study recognise its importance, cognitive and behavioural assessment is at present not provided to all patients and methods of evaluation are often informal.
3. Barriers exist to implementing screening programmes including a lack of resources, perceived attitudes of other staff members, and of patients and their families.
4. Increased resources, education, and psychology input may assist in overcoming these barriers and providing modern holistic care to patients and their families.

6.2. Introduction

Motor neurone diseases (MND) is an umbrella term for neurodegenerative syndromes marked by degeneration of the upper and/or lower motor neurons of the brain and spinal cord. Half of patients with MND die within 30 months of symptom onset, most commonly due to failure of the respiratory system. Amyotrophic Lateral Sclerosis (ALS), the most common form of MND, is classified by involvement of both the upper and lower motor neurons, presenting as muscle rigidity, wasting, and weakness (Strong et al., 2009).

However, in addition to the physical symptoms, it is now recognised that impairments in cognition and behaviour are common in patients with ALS. Difficulties in executive functions (e.g., problem solving, decision making, social perception), language (e.g., word finding, comprehension), and behaviours such as apathy are commonly reported (Raaphorst et al., 2012a; Beeldman et al. 2016). It is estimated that approximately 50% of ALS patients experience some

changes in cognition and behaviour, of which approximately 15% meet diagnostic criteria for frontotemporal dementia (Goldstein and Abrahams, 2013). A clinical, pathological, and genetic overlap has been established between and frontotemporal dementia confirming that the two conditions constitute a spectrum disease (Turner et al., 2013).

Changes in cognition and behaviour have important implications for patient management (Abrahams, 2013b) and have been associated with significantly shorter survival time in patients with ALS (Elamin et al., 2013; Caga et al., 2016). People with ALS and cognitive change have shown less compliance with life-prolonging interventions (Olney et al., 2005; Martin et al., 2014), and have a reduced ability to plan and organise medications (Stukovnik et al., 2010). Furthermore, behavioural symptoms are one of the greatest contributors to caregiver burden, perhaps over and above physical symptoms (Lillo et al., 2012b). Thus, the accurate and timely understanding of patients' cognitive and behavioural profile is of vital importance. Recently updated guidelines from the National Institute for Health and Care Excellence have incorporated recommendations for cognitive and behavioural assessment in patients with MND (NICE, 2016). These guidelines note that a patients' cognitive and behavioural status has implications for end of life planning, the type of medications that should be prescribed, the use of gastronomy, and the use of respiratory interventions. Additionally, discussions around care should be tailored to each person's needs, communication ability, cognitive status, and mental capacity (NICE, 2016).

Unfortunately, measuring cognition in patients with ALS has been historically difficult. Standardised cognitive screening, and neuropsychological

assessment more generally, rely on a person's ability to either speak or write their responses, often under timed constraints. Additionally, evidence suggests that clinicians are poor at detecting cognitive impairment using clinical judgement when compared to formal cognitive screening (Cohen et al., 1993; Crawford et al., 2001; Burleigh et al., 2002; Bouwmans and Weber, 2011; Mitchell et al., 2011), particularly in cases of mild cognitive deficits (Dungen et al., 2011). While no identifiable research is available on the practices of clinician's caring for patients with ALS, within elderly primary care settings some research suggests that cognition appears to be evaluated principally using clinical judgement. For example, Bush et al. (1997) found that 72.8% of primary care physicians evaluated cognitive status using clinical judgement while only 27.2% used a formal test. More recently, Galvin, Meuser and Morris (2012) found that formal screening tools, such as the Mini Mental State Examination, are used widely by healthcare professionals.

For patients with MND, tools such as the Mini Mental State Examination are not appropriate due to the requirement for intact motor skills. Fortunately, in recent years, a number of ALS-specific screening tools have been developed, most notably the ECAS (Edinburgh Cognitive and Behavioural ALS Screen; Abrahams et al., 2014) which has been validated on Scottish, German and Italian populations (Lulé et al., 2015; Niven et al., 2015; Loose et al., 2016; Poletti et al., 2016). The ECAS has been shown to be sensitive to cognitive impairment against extensive neuropsychological investigation (Niven et al., 2015) and is possible to administer in patients with even severe motor disability (Lulé et al., 2015). The ECAS is designed for use by non-neuropsychologist staff, such as doctors, clinical care specialists, and other medical professionals.

While the importance of understanding the cognitive and behavioural profile of neurological patients is clear, a number of barriers have been identified in the implementation of cognitive screening in primary care settings; for example, Bush et al. (1997) found that a lack of time, patients becoming offended or resisting, lack of proven benefit, and inadequacy of available tests all posed problems. Similarly, Boustani et al. (2005) identified increased time burden, no referral access to neuropsychology, patient refusal, and that physicians do not fully understand the operating characteristics of screening tests. Yet, more recently, Fowler et al. (2012) found that patient refusal of cognitive screening is low, and more unlikely in patients who perceive there to be benefits.

However, there exists a dearth of knowledge as to the attitudes and practices of Health Care Professionals (HCPs) in ALS services with regards to cognitive and behavioural screening.

The aim of this study was to explore HCPs' attitudes to screening, and more specifically, views on the importance of screening, practices around screening, and what barriers exist to the implementation of screening for cognitive and behaviour change in ALS in Scotland

6.3. Methodology

Structured interviews consisting of both open-ended and forced-choice questions were undertaken with participants. Thematic analysis was used to analyse the data. This study received ethical approval from the Psychology Research Ethics Committee of University of Edinburgh.

6.3.1. Participants

Participants were HCPs working with patients with ALS and recruited from 6 NHS health boards in Scotland. Fourteen HCPs took part in this study, including 5 ALS clinical care specialists, 5 neurologists (3 consultant neurologists and 2 specialist registrars in neurology), and 4 psychologists (2 clinical psychologists and 2 clinical neuropsychologists). Participants, on average, had spent 10.04 years in their current role, and an average of 11.64 working with patients with ALS. Clinical care specialists were recruited through MND Scotland, while neurologists and psychologists were recruited via chain-referral sampling methods.

6.3.2. Procedure

Participants were contacted by email and invited to take part in this study. Participants were given the option to complete the interview by telephone, in person, or to complete an online form. In all cases, questions posed to participants were identical. Twelve participants were interviewed by telephone, while two completed the online form. Those who chose the online form stated that this was due to time restrictions. Responses of participants who completed the online form did not thematically differ from those who completed an interview. Interviews were conducted between February and May 2015 and lasted approximately 20-30 minutes. Interviews were audio-recorded, transcribed verbatim (transcripts were anonymised to protect confidentiality), and subjected to thematic analysis. Thematic codes emerged post-hoc based on participant responses (see Table 6.1).

Table 6.1. Overview of analysis themes

Topic	Themes	Subthemes	Disciplines
Importance of screening	Care provision & planning	a. Person-centred care	All
		b. How staff communicate	All
	Capacity	a. Consent to interventions	All
		b. Power of attorney	CCS, Psychology
Barriers to screening	Staff barriers	a. Perceived unimportance	All
		b. Negative patient outcomes	All
		c. Lack of awareness	All
		d. Lack of confidence	All
		e. Who should administer?	Psychology
	Resources	a. Time	All
		b. Staff	CCS, Neurology
		c. Training/Education	CCS, Neurology
		d. ALS-Specific tools	Psychology
	Patient/family barriers	a. Refusal	CCS, Psychology
		b. Patient impairment	CCS, Neurology
Solutions to barriers	Increased resources	a. Increased education/training	All
		b. Increased psychology input	All
		c. Increased CCS staff	CCS, Neurology
	Standardisation	a. Screening as standard protocol	CCS, Psychology
	Other	a. Technology	CCS
		b. ALS-Specific Tools	Psychology

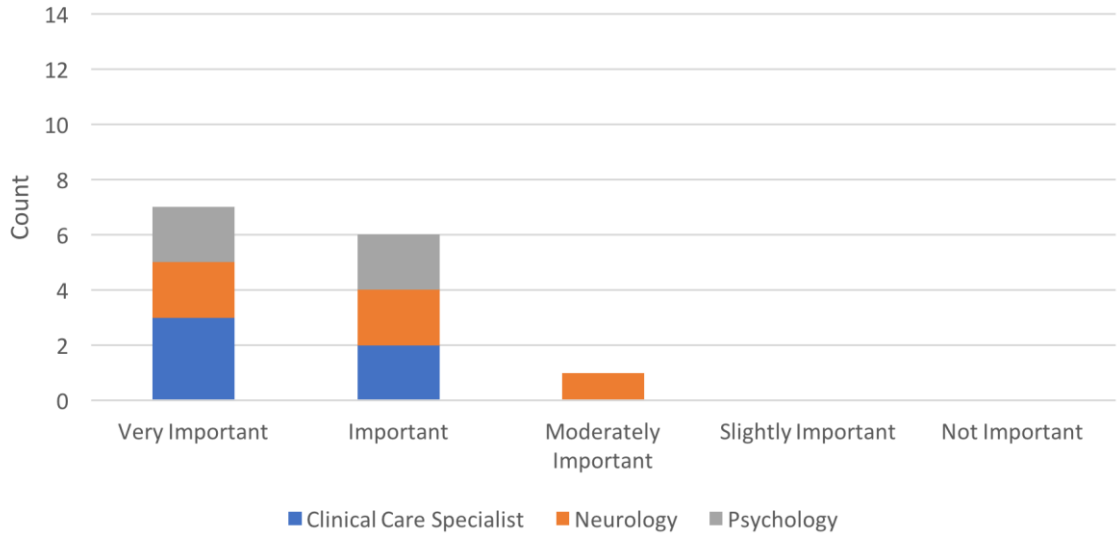
Note: CCS = Clinical Care Specialists, All = Clinical Care Specialists, Neurology, Psychology.

6.4. Results

6.4.1. Attitudes and practices to screening

Participants were asked how important they viewed screening for cognition and behaviour on a five-point Likert-type scale. Figure 6.1 shows that all but one participant believed screening to be either important or very important.

Figure 6.1. Perceived Importance of Screening



Participants were asked to qualify their judgement of perceived importance, and additionally, asked whether they perceived there to be benefits to screening. For participants who reported screening to be important or very important, two categories emerged for the importance of screening: a) care provision and planning, and b) decision making and mental capacity.

a) *Care provision and planning:* The majority of participants noted that screening allows HCPs to provide holistic, person-centred, and individualised treatment, as opposed to addressing ALS as solely a physical condition. Participants additionally reported that screening allows clinical staff to tailor the way in which they communicate with patients and with their families.

"Informing clinicians who are working with patients about what their needs actually are as opposed to just simply addressing this as a physical condition."

-Psychologist

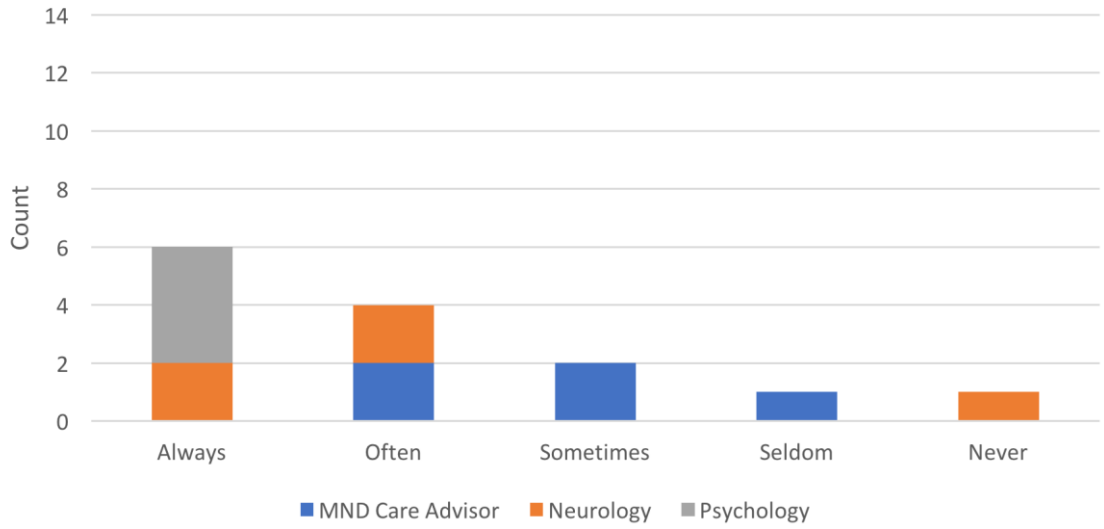
b) *Decision making and mental capacity:* Participants noted that screening assists in the determination of mental capacity and decision making abilities, which is important as there are end-of-life decisions to make, such as power of attorney, and that medical interventions can be invasive (for example, percutaneous endoscopic gastrostomy). As such, it is important that patients' capacity to consent is established.

"There's a lot of invasive medical procedures involved sometimes in ALS and you have to ask the question of whether the person's got capacity to make these decisions"

-Psychologist

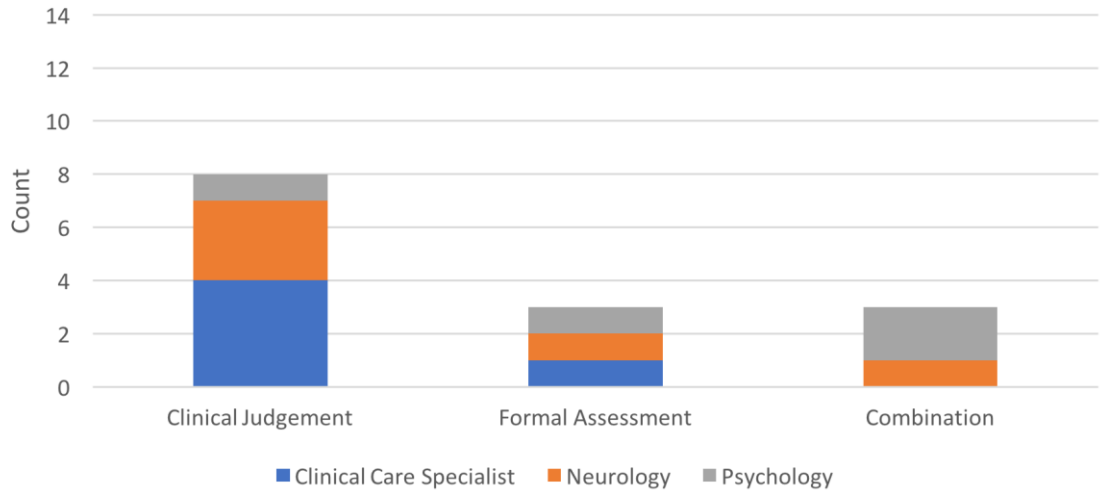
The methods by which HCPs screen for cognitive and behaviour change, and the frequency of such screening, were explored. Participants were asked a forced choice question as to whether all patients diagnosed with ALS should be screened for cognitive and behaviour change as standard. Of the 14 participants, 13 (92.86%) responded 'yes' and one participant responded 'no'. When asked how often participants in this study evaluated patients' cognitive and behavioural status, 71.43% stated always or often, 21.43% stated sometimes or seldom, with one participant never evaluating cognition and/or behaviour (Figure 6.2).

Figure 6.2. Reported Frequency of Cognitive & Behavioural Assessment



However, of the participants who did evaluate cognition and behaviour, 61.54% reported using their clinical judgement solely, with 38.46% using a formal screening tool, or a combination of a screening tool and clinical judgment (Figure 6.3). Neurologists, clinical care specialists, and psychologists all reported that cognitive and behaviour assessments was currently conducted within their discipline, suggesting no clear pattern as to who tends to perform such assessments.

Figure 6.3. Reported Methods of Assessing Cognition & Behaviour



6.4.2. Perceived barriers to screening

Participants were asked what, if any, barriers existed to the implementation of screening. From participants' responses, three categories of barriers were identified: a) staff-specific barriers, b) resource barriers, and c) patient/family barriers.

a) *Staff-specific barriers:* These concern other members of staff or disciplines reported by participants of this study. All of the participants in this study (i.e., all HCP disciplines) reported at least one barrier relating to other members of staff, in particular, that staff held negative attitudes toward screening. These attitudes include a perceived unimportance of screening, the perceived negative psychological impact that identifying a cognitive or behavioural deficit might cause to patients, a lack of clinician awareness of cognitive or behavioural change, a lack of confidence in administering screening, and concern around who should administer screening. One participant reported that clinical staff feel *"that it's not an important exercise to put patients through […] a sense that the physical*

wellbeing is sometimes more important than the emotional and cognitive wellbeing." -Psychologist

However, one of the most commonly cited staff-specific barriers was in reference to Neurology specialists, as opposed to other professions. For example, that Neurologists miss the subtleties of cognitive and behavioural change, and the effects that this can have.

> *"I mean even ten years ago people were told that well don't you worry because ALS doesn't affect the mind in any way. And in fact there are some consultants that still say that"*

b) *Limited Resources:* In addition to other staff, resources were commonly noted as a barrier to screening, in particular time, staffing levels, access to training, and appropriate assessment tools. Despite the desire to implement screening, the length of each consultation was deemed insufficient to administer formal screening. Moreover, staff viewed screening as a sensitive issue and that HCPs needed to build a rapport with the patient first, adding additional time requirements. Further to this, participants reported that insufficient training was provided in the administration of screening tools and that services were understaffed.

c) *Patients and families:* A number of participants, particularly psychologists, noted that patients themselves may be a barrier to screening, such that, patients and carers may refuse. Additionally, the presence of cognitive or behavioural symptoms was suggested to pose a challenge in and of itself. However,

participants expressed that this is a rare occurrence and that, in all cases, that this was only a perceived barrier, rather than from experience with patients.

> *"I think some of the barriers can be patients themselves not wanting to engage in it because it's another assessment tool that's highlighting weaknesses in their profiles…. for me, in my experience on the whole, I have not really found a lot of barriers in patients themselves."*
>
> *-Psychologist*

6.4.3. Suggested solutions

In addition to identifying barriers to screening, participants were asked if they had views on how barriers may be overcome. Three common solutions were offered by participants: a) increased education, b) increased psychology input, and c) screening all patients as standard practice. Three other solutions were also offered: increased number of ALS clinical care specialists, use of technology, and development of ALS-specific screening tools.

Most commonly, participants suggested that education may overcome barriers to screening. Education referred to patient/caregiver and staff. The majority of participants felt that it is important to increase awareness, highlight the benefits of screening, and increase the opportunities for formal training. Commonly reported, was that participants felt psychology should have a larger input into patient assessment, specifically, that dedicated psychologists should be part of the multidisciplinary team. However, some disagreement emerged as to who should administer screening. While neurologists felt that both clinical care

specialists and psychologists should be responsible, psychologists were sceptical of non-specialists administering cognitive/behavioural screening due to a lack of formal training and experience. Currently, participants in this study noted that screening was not specific to any one discipline.

An additional recommendation to increase screening in ALS was to make it standard practice for all patients and in so doing, patients may not feel singled out or at risk. Finally, other less-reported solutions include the increased staffing of clinical care specialists in Scotland, and the utilization of technology in interpreting formal screening tools.

6.5. Discussion

The aim of this study was to explore HCPs' attitudes to cognitive and behavioural screening in ALS. Fourteen HCPs were interviewed and asked their opinion as to the importance of screening, their practices around screening, and what barriers they perceive to exist. This study found that the majority of HCPs deemed screening to be important or very important due to its implications for care provision and end of life planning, and for issues surrounding decision making and mental capacity. Specifically, participants noted that assessment of cognition and behaviour allowed for the provision of person-centred, holistic and individualised treatment that sees MND as more than a physical disease. Given the rapid rate of disease progression, important decisions are necessary with regards to end of life planning and treatment. Thus, it is was seen as crucial to understand the ability of a patient to make such decisions, and what additional supports may be required to do so. These findings suggest that HCPs are largely

in agreement with the recently updated NICE guidelines on assessment and management of ALS (NICE, 2016).

Ninety-three percent of participants stated that screening for cognition and behaviour in ALS should be standard practice for all participants, but only 71.43% stated that they evaluate always or often. Of the HCPs who evaluated cognition and behaviour seldom or more frequently, only 38.46% reported formally evaluating cognitive and behavioural status of ALS patients using a screening tool.

The discord between attitudes and practice may be that in reality, HCPs are only formally screening patients when cognitive and behavioural symptoms are severe or overt, such as cases of comorbid dementia. Yet, the majority of patients with ALS will present with mild cognitive and behavioural changes that may not be explicitly evident on observation. Research has demonstrated that even mild changes can have significant impact on caregivers (Lillo et al. 2012b), affect the patients' ability to manage their medications (Stukovnik et al. 2010), and reduce engagement with life prolonging interventions (Olney et al. 2005; Martin et al. 2014). Therefore, it is important to offer screening to all patients, regardless of whether overt symptoms are present, closing the gap between attitudes and practice.

Even in those cases were cognition and behaviour is evaluated, clinical judgement is the most common method employed. Based on previous research citing the poor accuracy of clinical judgement to detect cognitive and behavioural impairment (e.g., Mitchel et al. 2011), and the frequency by which this method was employed by participants in this study, it is highly likely that patients with cognitive and behavioural changes are not being identified. With the development

of short ALS-specific tools such as the Edinburgh Cognitive and Behavioural ALS Screen, and the growth of multidisciplinary care systems, it should be possible for HCPs to include screening as standard practice for all patients. Given this, clinicians should be moving away from informal assessment and toward a standard screening procedure using a validated formal test.

6.5.1. Barriers to Cognitive and Behavioural Screening

When HCPs were questioned as to what barriers existed in implementing cognitive and behavioural screening, three themes were identified: a) staff-specific barriers, b) resource barriers, and c) patient/family barriers. While the majority of HCPs in this study believed screening to be important, all participants also noted that a significant barrier was other staff. Perceived unimportance, lack of awareness, and potential negative consequences to patients were cited as possible obstacles to the implementation of screening. In particular, participants reported that neurologists' attitudes posed a significant barrier. This perception may be a by-product from the current care structure of neurology-led clinics in which medical or palliative facets of care are prioritised. Moreover, as noted by participants, appointment times between patients and neurologists are short, and there may not be sufficient time for cognitive/behavioural symptoms to be evident. As such, the barrier may be the clinical context.

Participants in this study suggested that the perceived unimportance and lack of awareness may be ameliorated by staff educational programmes and awareness campaigns which highlight the importance of cognitive/behavioural screening in line with NICE Guidelines. HCPs in this study suggested that education may alleviate some of the barriers, which may take the form of clinical

training workshops, or continuing professional development courses. Galvin, Meuser and Morris (2012) demonstrate that a training programme targeted at HCPs can be effective in improving medical knowledge, confidence in diagnosis and treatment, and enhancing clinical practice. Staff-specific barriers may be partly explained by HCPs have insufficient training in how to practically incorporate a patient's cognitive and behavioural status into practice. Therefore, such training and educational opportunities for staff may help overcome a number of the barriers cited in this study; for instance, if clinicians were more aware of the benefits to screening, how to administer such a screen, and what to do with that information, the barriers of perceived unimportance, lack of awareness, and lack of confidence may be reduced.

Unfortunately, enhancing and increasing educational and training to staff is constrained by services already identified as under-resourced. HCPs here report having insufficient time, and insufficient staff numbers to implement screening for all patients. To fully adhere to NICE guidelines and provide cognitive and behavioural assessment to patients with MND, increased funding and resources may be unavoidable. However, it is possible that short-term funding solutions may provide initial increased education and training that could be maintained with normal resources thereafter.

However, there was disagreement among participants as to who should administer screening tools. A number of participants suggested that increased screening may be achieved by increased input from psychologists. This may mean psychologists undertaking the assessment themselves, or that psychologists provide supervision to non-specialist HCPs. A dual pathway model where both of these routes are operationalised would maximize the service to

capture a larger proportion of ALS patients, including both those who are willing to attend psychology services, in addition to those who do not want to or are unable to attend. Geographical, financial, and staffing restrictions may necessitate that individual health boards or centres operationalise screening programmes according to their unique capabilities.

Interestingly, HCPs expressed that patients and their families might themselves present a barrier to cognitive and behavioural screening. While this is possible, participants herein could not provide examples where this had actually occurred. In a large study of screening in primary care, Fowler et al. (2012) found that patient refusal was low (10.3%), and significantly less likely in those who perceive there to be benefits to screening. This concern may in fact reflect HCPs desire to avoid causing distress to patients by identifying a cognitive or behavioural symptoms. As such, this barrier may be perceived rather than based on actual practice or experience with patients and families and further research should address this issue.

The barriers which emerged in this study echo some of those previously reported specifically, lack of time and potential negative consequences to patients, clinicians' perceptions of screening instruments, and negative psychological outcomes for patients posed barriers. (Bush et al. 1997; Boustani et al. 2005) Thus, the barriers highlighted herein may not be unique to ALS services, but instead may be common to cognitive and behavioural screening generally and lessons can be learned from other setting in overcoming these barriers in ALS services.

While the results of this study provide the first insights into screening practices and HCP attitudes in Scotland, the sample size for this study was small,

and incorporated opinions from different professions working in different health boards. While this provides a diverse range of opinions, it is not possible to determine whether the opinions of one profession or health board will translate to another. Further research is required to better understand whether these results generalise to the larger HCP workforce in ALS services and to explore whether consensus can be agreed. Additionally, the interviews in this study were conducted prior to the release of the NICE guidelines, and as such, it is unclear whether these new guidelines could directly impact on service provision.

6.5.2. Conclusions

Cognitive and behavioural screening should be an integral aspect of care services provided to patients with ALS. While clinicians in this study recognised the importance of cognitive and behavioural assessment, not all patients are being offered this service. Furthermore the use of clinical judgement rather than screening tools may provide a false estimation of patients' abilities. HCPs in this study identified that barriers exist to cognitive and behavioural screening in the form of other members of staff, a lack of resources, and in patients' themselves and their families. When examining the barriers to screening, increasing education and training to staff, and increased psychology input may, in turn, increase HCP awareness, increase the perceived importance of screening, and increase non-specialists' confidence in the administration of standardised screening. Additionally, making screening standard to all patients, a belief held by 93% of HCPs in this study, may reduce the likelihood of causing distress to patients and their families and ensure that MND patients receive appropriate care provision and planning. While individual health boards may require different

approaches to adequately implement screening programmes, a national strategy may be required to ensure consistency and equality of care provision.

Chapter 7 demonstrates that clinicians recognise the importance of cognitive and behavioural screening, but that it may not be common practice and important barriers exist to the implementation of neuropsychological screening as standard practice. These barriers include staff, resources, and issues concerning patients and their families. As such, Chapter 7 addresses Aim 4; names, to explore clinicians' attitudes and practices around cognitive and behavioural screening in ALS.

CHAPTER 7: General discussion

The central aim of this research was to examine the evolution of cognitive and behavioural functioning over the course of ALS, and provide a means of longitudinal assessment. Specifically, this research aimed to: 1) develop alternate forms of the Edinburgh Cognitive and Behavioural ALS Screen to accommodate repeated longitudinal assessment in ALS; 2) examine how cognition and behaviour relate to clinical disease stages in ALS; 3) evaluate how cognitive and behavioural symptoms evolve over the course of the disease in ALS; and 4) explore clinicians' attitudes toward cognitive and behavioural screening in ALS. These aims will be discussed in the context of the novel findings presented herein, followed by a discussion of how these aims interrelate and future directions of the field.

7.1. Cognitive assessment in ALS

Historically, cognitive and behavioural research in ALS has been impeded by the use of assessment tools which do not accommodate physical disability. Many common cognitive tasks, for example, the Trail Making Test and verbal fluency tests, rely on intact motor speed. Muscle wasting and weakness, a hallmark of ALS, can exaggerate impairment or imply impairment where none exists. This is evident in research which has reported motor-corrected and uncorrected scores (Stukovnik et al., 2010). Conversely, the use of tests dependent on motor speed may also mask a decline in functioning such that patients with more severe concomitant physical and neuropsychological impairments are unable to complete the assessments. Fortunately, efforts have been made in recent years

to modify and develop novel assessment tools to account for motor speed in ALS.

The ECAS was designed specifically for ALS and is independent of motor speed. The ECAS measures cognitive domains commonly affected in ALS (executive functions, verbal fluency, language, social cognition) as well as those less commonly reported (memory and visuospatial functions), providing a comprehensive overview of cognitive functions (Abrahams et al., 2014). The ECAS additionally includes a caregiver behaviour interview based on diagnostic criteria for frontotemporal dementia. The ECAS has been successfully implemented in research and clinically, and has been translated and validated in numerous languages and demographics (Loose et al., 2016; Lulé et al., 2015; Mora et al., 2018; Niven et al., 2015; Pinto-Grau et al., 2016; Poletti et al., 2016; Ye et al., 2017). While the development and subsequent implementation of the ECAS has been successful in provided an accurate and rapid assessment of cognition and behaviour in ALS, limitations do exist.

Recent large-scale studies have begun to suggest that neuropsychological functioning may decline with disease progression (e.g., Elamin et al., 2013) suggesting that multiple regular assessments are necessary. There are three methods by which cognition can be assessed serially: a) administration of two different tests that purportedly measure the same cognitive domain(s), b) administration of the exact same test(s) on more than one occasion, or c) administration of a test that incorporates alternate forms.

Administering different cognitive tests at different occasions is problematic. The interpretation of change is limited and tests must be chosen which purportedly measure the exact same cognitive domain, in the same way,

and to the same degree. This method therefore assumes the presence of multiple competing but complementary assessment tools, which is not the case in ALS. The second method, administering the same cognitive test serially, suffers its own problems. Presenting patients with the same cognitive test more than once increases the well documented risk of practice effects, in which patients' performance improves over time due to learning test content or test-taking strategies. As with most cognitive tests, the ECAS has shown to have practice effects with repeated administration of up to one year (Burkhardt et al., 2017). These practice effects are problematic in that they provide an exaggerated estimate of current functioning, and may mask a decline longitudinally. Indeed, Burkhardt et al. (2017) found that practice effects with repeated administration of the ECAS were present for control participants but not for patients, which implies that patients may have declined over the study period but that this decline was obscured. It is possible to correct for practice effects statistically, assuming sufficient variability in scores and the presence of a representative control group. Unfortunately, ceiling effects exist within a small number of ECAS domains resulting in an inability to correct for practice effects statistically i.e., data cannot be accurately corrected statistically when censored. As such, the best option for repeated assessment in ALS is to develop alternate versions of the ECAS.

7.1.1. Summary of findings and discussion

A primary aim of this research was to develop alternate forms of the ECAS to accommodate repeated serial testing in ALS. Two alternate forms of the ECAS (B and C) were developed. The alternate forms of the ECAS were administered to five independent groups of healthy adults. One of these groups was used to

pilot and select appropriate stimuli, two were utilised to establish normative data, and two to evaluate the relative practice effects of using the same versus different versions of the ECAS. The findings of this study provided strong evidence of the equivalence of the alternate forms to the original ECAS-A, and in validating the amelioration of practice effects when using the alternate versions.

When administered to independent groups, matched by age, gender, and education to the control sample used in the ECAS validation study (Niven et al., 2015), all three ECAS forms were statistically equivalent. Indeed, no significant differences observed in domain scores, with Bayesian statistics provided evidence in favour of the null hypothesis (i.e., that the different forms come from the same sample). Cut-off scores demonstrated parity across versions and as such, with ECAS-A cut-off scores were retained for the alternate forms. Furthermore, significant practice effects were observed in using the ECAS-A serially whereas no significant improvement was found when using different versions. Finally, inter-rater reliability for all three versions of the ECAS was found to be excellent, suggesting that with appropriate training highly similar scoring outcomes are observed. These findings provide strong proof-of-concept evidence for the use of the ECAS in serially assessment. While this was an important step, to enable the interpretation of change on a case-by-case basis, further research was necessary.

Reliable change indices are statistical methods which evaluate normal variation over time (test-retest reliability, measurement error) and provide cut-offs for significant change (two-tailed 90% confidence interval). A further sample of healthy adults were recruited and administered the alternate forms of the ECAS over a clinically relevant interval of 4 months. Test-retest reliability was found to

be good over this interval (i.e., the majority of subtests scoring .70 or above) and again, no significant practice effects were observed. Four metrics of change were calculated (two reliable change indices and two regression-based methods) with cut-off values for all four methods provided. Given the similarity across the four methods, conservative recommendations for clinical use were provided i.e., a change of ≥ 8, ≥ 4, and ≥ 9 for ALS-Specific, ALS Non-Specific, and ECAS Total Score constitutes a statistically reliable change.

7.1.2. Comparison to previous cognitive tests incorporating alternate forms

Alternate forms have been developed for a limited number of common neuropsychological tests, including the Wechsler Memory Scale (Margolis, Dunn & Taylor, 2001; Sullivan, 2005), Symbol Digit Modalities Test (Benedict et al., 2012; Hinton-Bayre & Geffen, 2005), Trail Making Test (Wagner et al., 2011), Montreal Cognitive Assessment (Costa et al., 2012), Neuropsychological Assessment Battery (Yochin, Kane & Muller, 2009); Zgaljardic et al., 2013), and Rey Auditory Verbal Learning Test (Ryan et al., 1986). However, the methods used to evaluate the properties of these alternate forms has been inadequate and the methodological design implemented in the development of the ECAS-B and ECAS-C was intended to overcome these limitations.

The process by which alternate stimuli have been develop in other cognitive tests are rarely, if ever, reported. The evidence-based development of alternate stimuli for the ECAS was conducted through painstaking consultation and piloting processes in which the linguistic, physical, and cognitive characteristics of items were considered (see Appendix II for summary). Alternate forms have also largely been studied using undergraduate students (Sullivan,

2005), or using clinical populations such as depression (Ryan et al., 1986; Wagner et al., 2011), substance abuse (Ryan et al., 1986), neurodegenerative disease (Benedict, 2005; Costa et al., 2012b; Margolis, Dunn, & Taylor, 2001), and concussion (Hinton-Bayre & Geffen, 2005). This is problematic owing to the fact that the psychometric properties of a test (i.e., the equivalence of alternate forms) should be based on normal healthy performance and variation. The unique characteristics of different clinical syndromes limits the generalisability of a tests' psychometric properties to the cohort studied, and rarely are matched control groups included. Furthermore, some clinical populations would be expected to decline progressively and therefore confound the trajectory of data over repeated assessments. It is for these reasons that the ECAS was standardised on a sample of healthy older adult who reflect the demographic characteristics of ALS patients.

Most previous studies only include a single repeat testing group where participants are assessed serially. Alternate form equivalence cannot be determined from such a design due to the potential that some forms are more difficult (i.e., score reduction) but that practice effects persist (i.e., score increase) which statistically cancel each other out. In the ECAS, the alternate forms were presented to multiple independent groups who either completed a single version of the ECAS or multiple ECAS forms serially. For the groups who completed one ECAS form, no significant differences were observed across forms and for the group who completed the ECAS forms serially, no significant difference was observed between forms.

In addition to methodological oversights, very little previous research performed accurate statistical analysis. Commonly, Pearson correlation

coefficients (e.g., Yochin, Kane & Muller, 2009; Zgaljardic et al., 2013), t-tests (e.g., Costa et al., 2012b), and ANOVAs (e.g., Sullivan, 2005; Wagner et al., 2011) are used as evidence of equivalence. However, this is a fundamental misunderstanding of Null Hypothesis Significance Testing (NHST). NHST is based on the rejection or rejection failure of the null hypothesis and does not directly test the null hypothesis. In other words, a failure to reject the null hypothesis is not evidence *for* the null hypothesis. Most studies falsely claim that a non-significant t-test or ANOVA demonstrates alternate form equivalence. Furthemore, correlation coefficients do not demonstrate equivalence. Correlational analysis simple measures the strength of a relationship, not equivalence. For instance, if one test form is consistently more difficult than an alternate test form, these two will possess a high correlation despite potentially large mean differences. Finally, the majority of statistical tests used previously are comparisons of means. While this is an important metric, it does not measure distributional differences such as skew and kurtosis. Theoretically, two test forms could possess the same mean score but with differences in standard deviation and distribution shape. The statistical analyses conducted for the ECAS were chosen to overcome these limitations. ANOVA was implemented to evaluate whether significant differences exist in mean scores; Kolmogorov-Smirnov tests were implemented to determine whether significant differences exist in distributional shape; and Bayesian statistics were used to directly test the evidence in favour of the null hypothesis.

Thus, the methodological design of developing ECAS alternate forms overcomes the limitations present with other measures. Strong evidence of equivalence exists between forms, in addition to strong evidence that the forms

ameliorate practice effects in repeated assessment. Therefore, the ECAS-A-B-C provide an accurate and reliable method in measuring cognition in ALS longitudinally, and in interpreting change on a case-by-case basis.

7.2. Cognition across the ALS disease course

The question as to whether cognition and behaviour declines over the course of the disease in ALS has been unresolved. Small sample sizes and attrition reduce the power to detect mild changes, and not controlling for attrition results in only the healthiest participants remaining in the study (e.g., Elamin et al., 2013). Inappropriate disease metrics result in confounded measurement of cognition and a non-linear and variable measure of progression. Short test-retest intervals and limited follow-up occasions reduce the possibility of observing disease progression. The present study combined specific and standardised measures of cognition, behaviour, and disease progression to overcome issues with previous ALS studies. Participants were tested on four occasions every four months to maximise the possibility of detecting disease progression. The median disease duration for ALS is three years, and diagnosis occurs after approximately 12 months (Al-Chalabi & Hardiman, 2013). As such, a one year testing period represents approximately 50% of the remaining median disease course after diagnosis.

Cross-sectionally, neuropsychological functions were seen to relate to disease stage, with patients in more advanced disease presenting with worse cognitive and behavioural symptoms. Specifically, verbal fluency, apathy, loss of sympathy and empathy, perseveration, disinhibition, and hyperorality were more

impaired in later disease stages. This observed relationship was mediated or moderated by the presence of bulbar symptoms. Contrary to previous reports, bulbar onset patients were not more likely to have cognitive impairment, rather, the presence of bulbar features was an important factor. This may explain the inconsistently with which bulbar-onset has been linked with cognitive and behavioural impairment. Previous studies were confounded by the presence of patients with bulbar involvement in groups of spinal onset patients. As such, the onset of bulbar features in ALS may represent a unique turning point in the disease course. Current staging systems in ALS do not incorporate cognition and behaviour, however, the evidence here suggest that neuropsychological functioning should be an important consideration in future systems. Alternatively, or in addition, neuropsychological functioning may be included in functional rating scales such as the ALSFRS-R. Cognitive/behavioural impairment may simply represent an additional 'region' (in addition to upper limb, lower limb, bulbar, and respiration/nutrition) expanding King's staging to 5 stages. In such a case, a patient with cognitive impairment and bulbar involvement would be in Stage 2, progressing to Stage 5 at the onset of respiratory insufficiency.

However, given the decline in neuropsychological function, cognitive and behavioural *stages* reflective of impairment severity (e.g., mild, moderate, severe/FTD) may be practical. One study examined behavioural disease stages in ALS patients using the Frontotemporal Dementia Rating Scale (Hsieh, Lillo, Kiernan, Hodges & Mioshi, 2013). ALS patients' behavioural stages (30.8% mild, 63.1% moderate, and 6.2% severe) corresponded poorly to the ALSFRS-R suggesting that motor and neuropsychological symptoms progress at different rates requiring the assessment of both. The King's Clinical Disease Stage could

be expanded in an ‘ABC’ manner (i.e., A = ALS disease stage, B = Behavioural impairment, C = Cognitive impairment). For instance, a patient in King’s Clinical Stage 2 with mild cognitive impairment and no behavioural features would be classified as A2B1C0. How such a system would relate to the disease course as per Roche et al. (2012) remains to be seen.

Longitudinal results corroborate the findings of our cross-sectional analysis. ECAS Total, ALS Specific, and fluency were shown to decline significantly over the course of the study. Latent growth curve models (LGCMs) that accounted for non-random attrition were utilised, with attrition predicted by disease severity and neuropsychological impairment. As such, the analysis in this study was the first to produce unbiased estimates of change which has been lacking previously. This is evidenced by examination of the raw scores of patients over time which, when unadjusted, suggests no change or even improvement over time. Furthermore, no study to date has used neuropsychological evaluations that are not biased by motor impairment or practice effects. The development and utilisation of the ECAS alternate forms reduces the potential for practice effects, pervasive in many previous longitudinal studies.

While the observation of a significant decline in cognitive functioning over time is important in its own right, of value is the relationship observed between longitudinal neuropsychological functioning and disease stage. Disease duration (i.e., time), is of little clinical value in prognosis of patients with ALS. Disease stage, conversely, is a standardised metric which is not dependent on time, but represents a measure of each persons’ disease course. When disease stage was modelled, it captured and explained the effect of time with all cognitive and behavioural domains significantly affected. As with the cross-sectional analysis,

ALS Specific and Non-Specific functions reacted to disease stage differently. ALS Specific functions declined with disease stage early and quickly, while ALS Non-Specific functions declined more slowly and were dependent on baseline performance. Longitudinal data, when re-organised to directly assess the effect of disease stage, resulted in similar findings as our cross-sectional analysis. ECAS Total, ALS Specific, and behavioural features were found the decline linearly with disease stage. Of novelty however, ALS Non-Specific functions were longitudinally related to disease stage quadratically. This is explained by a 'turning point' at Stage 3 to Stage 4 re-iterating the importance of end-stage disease, and therefore respiratory involvement, in ALS Non-Specific trajectories.

Additional relationships were found between baseline ALS Specific neuropsychological functioning and age of onset, years of education, and the presence of the C9of72 expansion. Longitudinal decline was additionally related to these variables, however, years of education was predictive of behavioural, rather than cognitive decline. As such, these variables represent risk factors for worsening cognitive and behavioural performance, even after accounting for disease stage. The relationship between education, C9orf72 status, and ALS specific neuropsychological functions has been previously suggested. For example, Beeldman et al. (2016) found that fewer years of education was related to impairment in executive functioning, while the presence of C9orf72 repeat expansion has been consistently related to worse cognitive and behavioural performance (e.g., Byrne et al., 2012; Ratti et al., 2012; Snowden et al., 2013). ALS Non-Specific functions were less dependent on model covariates, suggesting that they are perhaps secondary to ALS Specific functions, or dependent largely on advancing disease processes. The current findings

reiterate the role that the C9orf72 expansion plays as a risk factor in ALS specific cognitive and behavioural decline. The significant effect of education on baseline levels and decline in behavioural functioning possibly indicate behavioural reserve (Kaplan et al., 2009; Premi et al., 2013; Stern, 2009).

Cross-sectionally in Stage 4, 80% of our patients experienced cognitive or behavioural impairment, while re-organisation of longitudinal data similarly found 72% of Stage 4 patients impaired. This point has important clinical implications. Stage 4 is defined by the need for nutritional or respiratory intervention. At this point in the disease, numerous important disease-specific decisions are expected of people with ALS, including life-prolonging interventions and power of attorney. ALS patients are regularly recruited into research studies, including clinical trials, and asked to make decisions about genetic testing. However, given the rates of cognitive and behavioural impairment present in ALS, the ability to make such decisions has yet to be fully explored, nor whether cognitive and behavioural impairment affects initiation of and adherence to medical intervention. The UK's Mental Capacity Act (Department of Health, 2005), and more recently, the Irish Assisted Decision-Making Act (Health Service Executive, 2015) describe decision-making capacity as the ability to understand, retain, use, and communicate information. These abilities rely on the neuropsychological domains of memory, executive functioning, and language abilities. The prevalence of impairment in these domains in ALS raises concerns as to patients' ability to make and communicate decisions and engage appropriately with medical care and research.

Paradoxically however, decisions about medical treatment are often made when patients are least likely to be capable of making such decisions.

Behavioural change, in particular apathy (Caga et al., 2016), and cognitive change, in particular executive dysfunction (Elamin et al., 2011), have shown to be negative prognostic indicators in ALS, with a reduction in survival time of approximately one year. While this may suggest that neuropsychological impairment represents an ALS phenotype with a more rapid disease course, it is also possible that cognitive and behavioural impairments are moderating the disease course by affecting the uptake of medical treatments, or the adherence to recommendations. ALS patients have been shown to be less compliant with respiratory and nutritional interventions (Olney et al., 2005; Martin et al., 2014; Chio et al., 2012) and less able to schedule medication use (Stukovnik et al., 2012). These results highlight the potential impact that declining cognitive impairment can have on intervention engagement, compliance, and survival; however, this area has yet to be robustly investigated. These results call into question the implications of neuropsychological impairment on patients' ability to negotiate social, medical, and legal aspects of their illness. Clinicians should therefore be cognizant of the effect that disease stage has on neuropsychological functioning, particularly in patients testing positive for the C9orf72 expansion, and the effect this may have on medical decision making and treatment compliance.

The patterns observed cross-sectionally and longitudinally suggest a different pattern of change for different cognitive domains, such that functions typically associated with the prefrontal cortex (e.g., verbal fluency) decline at Stages 2-3, whereas temporal-lobe mediated functions (e.g., memory) decline at Stages 3-4. This pattern follows the same neuropathological staging suggested by Brettschneider et al. (2013). Here, TDP-43 depositions in the prefrontal cortex were described in Stage 3 while pathological depositions in the hippocampus

were described in Stage 4. The pattern in our results may reflect underlying pathological disease spread expressing as cognitive dysfunction. The King's Clinical Disease Staging may be temporally related to pathology such that the King's Stages occur at similar times to the pathological stages. However, without corresponding imaging data this hypothesis cannot be tested.

7.3. Clinician's attitudes to neuropsychological screening

As previously noted, cognitive and behavioural impairment have important clinical implications to patients with ALS and their caregivers. Behavioural symptoms in ALS have been associated with increased caregiver burden (Andrews et al., 2017; Chiò et al., 2010), quality of life and depression (Chiò, 2010), activities of daily living (Mioshi et al., 2012), and relationship intimacy (Goldstein et al., 1998), over and above the impact of physical disability (Lillo et al., 2012b; Tremolizzo et al., 2016). While little research has been conducted on the impact of cognitive impairment, Goldstein, Atkins and Leigh (2002) found that subjective cognitive lapses negatively impact patients' quality of life. Furthermore, cognitive and behavioural impairment has been linked to negative medical outcomes, including worse prognosis and reduced uptake and adherence to medical interventions (e.g., Caga et al., 2016; Chiò et al., 2012; Elamin et al., 2011; Martin et al., 2014; Olney et al., 2005). Given the impact that neuropsychological impairment can have on the ALS disease course and psychological health of patients and their families, surprisingly little research is available on clinicians' attitudes and practices toward screening. The aim of this study was a first step in addressing this gap in the literature.

7.3.1. Summary of results and discussion

Participants of this study (Neurologists, Psychologists, and Clinical Care Specialists) noted that cognitive and behavioural screening in ALS is important in providing holistic person-centred care and in relation to decision making capacity. Indeed, all but one participant noted that screening should be standard practice to all patients. In contrast, less than half of participants stated that they always screen for neuropsychological symptoms, and when screening does occur, the majority of clinicians use their clinical judgement. However, there exists no evidence as to the accuracy of clinicians' judgement in assessing neuropsychological impairment. Certainly, evidence from other areas would suggest that clinical judgement has poor accuracy in detecting cognitive impairment.

Bouwmans and Weber (2012) examined the accuracy of neurologists' evaluation of cognitive impairment against a formal neuropsychological assessment in Parkinson's disease. The authors found that the sensitivity of neurologists in detecting cognitive impairment was low (33%), the agreement between neurologists was .74 (Kappa value), and the agreement between neurologists and patients' own evaluations was low (Kappa = .39). In a meta-analysis of available literature, Mitchell, Meader and Pentzek (2011) examined GP's ability to recognise cognitive impairment from clinical judgement. The accuracy in the recognition of dementia against a formal diagnostic interview was 73%. However, this reduced to 45% for mild dementia or mild cognitive impairment. Against a formal neuropsychological assessment, sensitivity of clinical judgement was 63% with 93% specificity. Therefore, while detection of

neuropsychological impairment in the extremes was reasonably accurate, in cases of milder impairment, clinicians' accuracy was poor. This is important given the predominantly mild cognitive and behavioural impairment observed in ALS.

Participants in the present study noted important barriers to cognitive and behavioural screening, specifically, that other members of staff held negative attitudes to screening. Negative attitudes were commonly attributed to neurologists, which poses a difficulty given the neurology-led services present in the UK health service.

Additional barriers include a lack of resources such as time, staffing, training, and appropriate assessment tools. As such, clinicians report that cognitive and behavioural screening is not common practice in ALS care services, that clinicians hold negative attitudes toward screening, prefer to use their judgement, but that this judgement is likely inaccurate. This is particularly pertinent given the findings presented in Chapters 4 and 5, which suggest that cognitive and behavioural impairment declines over the course of the disease. If clinicians are not measuring or accurately detecting impairment, and this impairment is progressive, it is unlikely that the cognitive and behavioural needs of patients with ALS and their families are being met through current clinical practice. Furthermore, if cognitive and behavioural impairment interacts negatively with medical care, it is possible that the care that is provided is being undermined. Given the ubiquity with which the ECAS and other screening instruments are present in the literature, there is a discord here between availability of assessment tools and clinicians' knowledge. Participants believed that increasing education, psychology input, and making screening standard to all patients would help overcome these barriers. However, the availability of the

ECAS and its ongoing development already provides an avenue for increasing assessment procedures. Perhaps, better promotion and training of the ECAS would help increase the frequency and improve the methods by which cognitive and behavioural health is addressed clinically.

7.4. Strengths, limitations, and future directions

The present research is the first to explore cognitive and behavioural change longitudinally. However, the cognitive and behavioural features in ALS remain heterogeneous and more work is needed to understand why some patients experience neuropsychological deficits while others do not. The present findings of a decline in cognitive and behavioural functioning across a standardised metric of disease progression is novel. However, not all patients presented with cognitive or behavioural impairment. Patients who do and do not experience neuropsychological impairment may possess distinct neural correlates or patterns of progression; for instance, whether ALS begins in the prefrontal cortex and spreads in a caudal fashion toward to motor cortex. Indeed, the present study demonstrated that cognitive and behavioural impairment can occur very early in the disease, potentially before the onset of motor symptoms. Neuroimaging studies, combining staging and the ECAS may elucidate subgroups which are yet unidentified, in addition to explaining the involvement of ALS non-specific functions.

Studies exploring the atypical presentation of cognitive dysfunction are relatively uncommon, particularly concerning memory and visuospatial functioning. Degeneration of the temporal lobes support this proposition (see

Chiò et al., 2014), in addition to pathological observations of hippocampal involvement in end-stage disease (Brettschneider et al., 2013). Alternatively, respiratory dysfunction resulting in hypoxia may also impact memory functions in late-stage patients. While the effect of respiratory insufficiency in ALS has previously been examined (Newsom-Davis et al., 2001), the evidence is lacking and no real progress has been made in almost two decades. Therefore, the impact of respiratory function on cognition and behaviour may explain some of the observed heterogeneity. The findings herein suggest that memory functions may be compromised, particularly in end stage disease, and predicted by baseline ability. Further research is required, which does not explicitly exclude end-stage patients, in order to profile the late-stage cognitive and behavioural changes associated with ALS. Moreover, it is possible that memory and visuospatial deficits are largely due to a cross-over effect from other cognitive domains. The degree to which cognitive domains are affected by primary deficits in ALS specific functions (e.g., executive functioning, language, fluency) remains unclear. Longitudinal studies, using appropriate and detailed cognitive tests, while controlling for interference from other cognitive domains are also needed. The overlap in cognitive and behavioural decline additionally highlights the need for a better understanding of the underlying mechanisms of behavioural change in ALS, and whether cognitive and behavioural symptoms represent truly distinct categories.

The evolution of behaviour longitudinally has largely been ignored in research. A novelty of this research is in the examination of behaviour longitudinally, and the exploration of individual behavioural domains. One of the main difficulties in behavioural research in ALS is the imprecise way in which

behaviour is measured. There is a lack of high standard and externally validated measures of behaviour in ALS. Questionnaires suffer from imposing limitations to the presentation of very particular behaviour symptoms. While the ECAS behaviour interview overcomes this issue, interview-based assessments introduce researcher variability. No current scale examines an appropriately extensive list of behaviours, address how long behaviours have been present, the frequency and severity of such behaviours, and provide information on overall behavioural impairment and individual behaviour-specific metrics – all of which are of interest. It is possible that exploring the mechanisms behind behaviours, and the cognition-behaviour relationship, may provide more objective measures of behavioural function.

Much of the literature has focused on the profile of cognitive and behavioural impairment, but relatively little has been done on the impact of mild neuropsychological dysfunction on patients' day-to-day lives. It is understood that behavioural symptoms can impact caregiver burden (Andrews et al., 2017; Chiò et al., 2010; Tremolizzo et al., 2016), quality of life and depression (Chiò, 2010), and that executive dysfunction is a negative prognostic indicator (Chiò et al., 2012; Elamin et al., 2011; Gordon et al., 2010b; Gordon et al., 2011; Hu et al., 2013). However, the extent to which neuropsychological symptoms impact activities of daily living, medical decision making, or adherence to medical recommendations is unresolved. One study (Mioshi et al. 2012) found that behavioural symptoms did impact on activities of daily living, but it is not known whether the same is true for cognition, nor which specific behaviours are responsible.

An additional strength and novel aspect of this research was in controlling for attrition and the use of the ECAS's alternate forms, which have biased previous longitudinal studies. Attrition was indeed acceptable in the present study, yet patients who continued participating were less likely to demonstrate disease progression (i.e., transitioning to more advanced stages). The bias introduced by attrition was controlled for using advanced structural equation modelling. However, the power to detect changes across disease stage was reduced. The ECAS and its alternate forms was chosen as it is specific to ALS and reduces the burden of participation, thereby minimising potential attrition and practice effects. Given the evidence of equivalence between forms, the assumption may be made that sensitivity and specificity data also transfers across test forms. However, future developments of the ECAS may include full neuropsychological validation of the alternate forms to confirm this.

As such, the present study supports the need for timely and ongoing assessment of neuropsychological impairment in ALS. Yet, the practices and attitudes of clinicians in implementing such procedures was unexplored. The barriers to cognitive and behavioural screening noted in Chapter 7 may additionally necessitate the development of an ECAS short form, or digital test, to maximise its use in busy clinic environments. Conversely, there exists no comprehensive and internationally agreed test battery for ALS. Therefore, the ECAS may also benefit from extension in situations when a more detailed evaluation is required. Such a development may see the lengthening of current subtests and the inclusion of novel tasks based on research developments, while retaining its strength as a motor-free assessment. This may address the ceiling

effects present in some subdomains of the ECAS, particularly language and visuospatial functions.

7.5. Conclusion

When appropriately specified models are estimated, cognitive and behavioural functioning are seen to decline, particularly with disease stage. Advanced disease stage, fewer years of education, and the presence of the C9orf72 expansion may be considered risk factors for declining neuropsychological abilities. As such, decisions about medical care should be made early in the disease to maximise the potential for capacity. The newly developed ECAS alternate forms provide a method by which neuropsychological functioning can be measured longitudinally. However, further outreach and resources may be required in order to maximise the inclusion of cognition and behaviour in the clinical care management of patients with ALS. In doing so, the quality of care provided to patients and their families will be improved, and the focus of care will be more holistic and representative of patients' experiences of ALS.

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Appendices

Appendix I: Summary of neuropsychological studies in ALS

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Abrahams et al. (1997)	52 ALS (24 with pseudobulbar ALS & 28 without) & 28 controls	Fluency (letter); Executive (planning: Tower of Hanoi; concept formation: WCST errors and categories); language (word recognition: RMT). NOTE: Impairment more pronounced in those with pseudobulbar ALS	Memory (Paired Associates Learning Test, KOLT); social cognition (RMT); object memory (KOLT); Executive (inhibition/attention: Stroop)	✓	✓	✓	✓	✓		
Abrahams et al. (2000)	22 sporadic ALS & 22 controls	Fluency (letter and category - animals)	Fluency (design, category); language (naming: GNT; word generation: Hayling Sentence Completion part A)		✓		✓			
Abrahams et al. (2004)	28 sporadic non-demented ALS & 18 controls	Fluency (letter: spoken and written); memory (letter span); language (GNT)	Fluency (category and design); executive functioning (ECST, PASAT); memory (Paired Associate Learning, Recognition Memory Test, KOLT); language (Hayling Sentence Completion part A); visuospatial (BLOT).	✓	✓		✓	✓	✓	

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Ash et al. (2015)	26 ALS (3 with FTD) & 19 controls	Fluency (letter); memory (forward digit span). ALS produced fewer words, more articulation errors, and fewer well-formed grammatical sentences. NOTE: Same population as ASH et al. (2014).	Executive (working memory: Reverse digit span); language (BNT); fluency (category). No difference for frequency of verbs or nouns produced per 100 words.	✓	✓		✓	✓		
Burke et al. (2016a)	59 ALS (20 bulbar onset, 39 limb onset) and 59 controls	*Patients vs controls:* Fluency (letter and category); executive (working memory: backward digit span) *Bulbar vs Limb*: social cognition (RME)	*Patients vs controls:* Executive functions (Brixton Spatial Anticipation Test; Stroop); social cognition (Judgement of Preference Test; RME); memory (forward digit span) *Bulbar vs Limb:* Executive functions (Brixton Spatial Anticipation Test; Stroop; backward digit span); memory (forward digit span); fluency (letter and category); social cognition (Judgement of Preference)	✓	✓	✓		✓		
Burke et al. (2016b)	106 ALS & 50 controls	Social cognition (Emotional recognition: RME) - (observed in ALS with concomitant executive dysfunction)		✓		✓				

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Carluer et al. (2015)	23 non-demented ALS, 45 controls (23 for cognitive tests & 22 for imaging)	Executive functions (switching/attention: TMT B-A; inhibition: Hayling sentence completion); fluency (VFI); social cognition (cognitive ToM: original false belief task). NOTE: ToM deficits significantly associated with executive functioning, and dorsomedial and dorsolateral prefrontal cortices using imaging techniques.	Executive functions (working memory: letter-number sequencing from WAIS)	✓	✓	✓	✓			
Cavallo et al. (2011)	15 ALS (6 with bulbar signs, 9 without) & 22 controls	Fluency (letter); language (GNT); social cognition (ToM: story completion - social context)	Fluency (category); visuospatial (VOSP); executive functions (Hayling Sentence Completion test part A and B; Brixton Spatial Anticipation); social cognition (ToM: RME; Story completion - non-social context). NOTE: No difference in ToM performance between patients with and without bulbar signs.	✓	✓	✓	✓		✓	

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Christidi et al. (2012)	22 non-demented ALS & 22 controls	Executive functions (Selective attention/inhibition: Stroop); Memory (immediate and delayed recall, memory encoding and consolidation: RAVLT)	Memory (retrieval: RAVLT)	✓				✓		
Crespi et al. (2014)	22 non-demented, C9-, sporadic ALS (19 included in imaging study) & 55 controls	23% classified as ALSci, 9% as ALSbi, 4% ALScbi, 64% intact. Social cognition (emotion recognition: Ekman Faces - Anger, disgust). Findings related to right lateralised microstructural changes in white matter tracts connecting frontal, temporal and occipital lobes.	Social cognition (emotion recognition: Ekman faces - sadness, surprise, happiness, fear)			✓				✓
Cuddy et al. (2012)	19 ALS & 19 controls	Social cognition/memory (Emotional memory: Brierley-Medford Sentence Task; Phelps Recall Task). 42% impaired on emotional word recognition on Brierley-Medford Sentence Task, 32% impaired on positive word recall (Phelps positive word recall task)	Memory (immediate and delayed, free and cued recall, recognition: CVLT)			✓		✓		

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Fiori et al. (2013)	23 ALS & 23 controls	Visuospatial (Hand Laterality Task)	Visuospatial (Mirror letter discrimination task)						✓	
Gibbons et al. (2007)	16 non-demented ALS & 16 controls	Fluency (category); executive (inhibition/attention: Stroop); Social cognition (ToM: cartoons and stories, mental and physical conditions). NOTE: Social cognition strongly related to executive functioning	Language (GNT); visuospatial (VOSP); memory (Hopkins Verbal Learning); executive (concept formation: WCST); fluency (letter)	✓	✓	✓	✓	✓	✓	
Girardi et al. (2011)	Study A: 19 non-demented sporadic ALS & 20 controls Study B: 14 non-demented sporadic ALS & 20 controls	*Study A*: Executive functions (affective decision making: IGT). NOTE: Affective decision making related to behavioural executive dysfunction (FrSBe) *Study B:* Memory (immediate recall: WMS); language (GNT); social cognition (ToM: Judgement of preference Task - social condition; emotion recognition: Facial Expressions of Emotions Test)	*Study A:* Language (GNT); fluency (letter) *Study B:* Memory (delayed recall - WMS, KOLT); executive (inhibition: Hayling Sentence Completion; Brixton Spatial Anticipation Test); fluency (letter); social cognition (ToM: Judgement of preference Task - control condition; emotion recognition: RME - marginal)	✓	✓	✓	✓	✓		

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Grossman et al. (2008)	34 ALS (includes unspecified number of ALS-FTD)	Cognitive impairment at 35.3%. Composite action and object word abilities generated (matching verb/noun with appropriate picture and matching verbs/nouns with description). ALS performed poorly on measures of action knowledge relative to noun knowledge.					✓			✓
Hammer et al. (2011)	20 ALS & 20 controls	Language (WAIS vocabulary subtest); fluency (Ruff Figural: strategies, letter)	Executive functions (working memory: digit span, reading span; concept formation: WCST; attention/inhibition: TAP)	✓	✓		✓			
Hanagasi et al. (2002)	20 sporadic ALS & 13 controls	Executive functions (working memory/attention: backward digit span, Continuous Performance Test; Delayed Recognition Test, Serial Digit Learning Test, Stroop, Trail Making B-A); fluency (letter and category); Language (BNT); Memory (delayed recall: CVLT); Visuospatial (BLOT, WAIS Block Design)	Memory (forward digit span; immediate recall, intrusions, recognition: CVLT, face recognition: Benton Facial Recognition)	✓	✓		✓	✓	✓	

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Hartikainen et al. (1993)	24 ALS, 22 PD, & 26 controls	ALS vs controls: visuospatial (Digit Symbol and Block Design); executive functions (attention/switching: TMT A-B); memory (list learning, immediate story recall)	ALS vs controls: memory (delayed story recall); fluency (category)	✓	✓			✓	✓	
Kasper et al. (2015)	98 ALS & 70 controls	41.4% cognitively impaired based on Strong Criteria. Most common impairment in executive functioning: shifting (TMT, fluency letter and category); initiation (fluency letter and category); memory (learning: Verbal Learning and Memory Test, CVLT)		✓				✓		✓
Kasper et al. (2016)	93 ALS (17 with UMN dominant, 16 with LMN dominant) & 73 controls	19.35% cognitively impaired, 4.3% ALS-FTD, 65.59% unimpaired.								✓
Lange et al. (2016)	20 ALS (1 with FTD) & 21 controls	Executive functions (perseverative and rule errors: WCST)	FAB, ECAS (ALS Specific and ALS Non-Specific); Executive Functions (WCST: total score)	✓						

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Lepow et al. (2010)	49 ALS (36 underwent detailed neuropsychological assessment: 13 were intact, 17 mild impairment, 7 FTD) & 25 controls	*ALS vs Controls:* Fluency (letter & category fluency total score). *ALS intact vs ALS mild vs ALS-FTD:* difference in letter and category fluency, number of clusters and switches for letter fluency, size of clusters for semantic fluency. Impairment shows gradient in line with cognitive grouping.	*ALS intact vs ALS mild vs ALS-FTD*: size of cluster for letter fluency, number of clusters and switches for category fluency		✓					
Leslie et al. (2015)	36 ALS (19 with ALS-FTD); 22 SD, & 26 controls	*ALS vs Controls:* ACE-R (Attention; memory; fluency VFI; language) - SYDBAT (naming; comprehension) *ALS-FTD vs Controls:* ACE-R (attention; memory; fluency; language; visuospatial); SYDBAT (naming; comprehension; semantic associations) *ALS vs ALS-FTD:* ACE-R (attention; memory; fluency); SYDBAT (naming; comprehension; semantic associations). NOTE: 35.7% ALS and 78.9% ALS-FTD had semantic impairment.	*ALS vs Controls:* ACE-R (visuospatial); SYDBAT (semantic associations) *ALS-FTD vs Controls:* ACE-R (none) *ALS vs ALS-FTD:* ACE-R (visuospatial)	✓	✓		✓	✓	✓	

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Libon et al. (2012)	41 ALS	Executive functions (concept formation: D-KEFS free and recognition sorting)		✓						
Lillo et al. (2012)	20 ALS, 20 FTD, 20 controls	*ALS vs Controls:* Executive functions (Inhibition: Hayling Sentence Completion Test; decision making: IGT) *ALS vs FTD:* inhibition Executive functions (Hayling Test) *FTD vs Controls:* executive functions (working memory: digit span backward; inhibition: Hayling Test; decision-making: IGT); emotional recognition	*ALS vs Controls:* Executive functions (working memory: Digit span backwards; decision-making: Iowa Gambling)); social cognition (emotion recognition: Ekman faces - marginal) *ALS vs FTD:* executive functions (working memory: digit span backwards; decision-making: IGT); social cognition (emotion recognition: Ekman faces - marginal) *FTD vs Controls*: executive functions (decision making: initial trials of IGT) NOTE: No effect of site of onset	✓		✓				
Lulé et al. (2005)	12 sporadic ALS & 18 controls.	Fluency (design); processing speed (SDMT); social cognition (emotional processing: international Affective Picture System - increased positivity, reduced arousal)	Fluency (letter); executive functions (concept formation: WCST)	✓	✓	✓				

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Machts et al. (2014)	40 ALS (3 with FTD); 39 amnestic MCI, 40 controls	*ALS vs Controls*: fluency (letter and letter alternation); memory (recognition: RAVLT); visuospatial (ROFCT) *ALS vs MCI:* visuospatial (ROCFT)	*ALS vs Controls:* executive functions (working memory: digit span backwards; cognitive flexibility: TMT B-A); memory (learning, immediate and delayed recall: RAVLT; digit span forward) *ALS vs MCI:* fluency (letter and letter alternation); cognitive flexibility (TMT B-A); working memory (digit span backward); memory (RAVLT: learning, delayed and immediate recall, recognition; digit span forward)	✓	✓			✓	✓	

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Massman et al. (1996)	146 sporadic ALS	Based on normative percentiles, patients scored the lowest on verbal fluency (FAS), immediate recall (CVLT) and attention (VSAT time to complete). Performed relatively well on recognition memory (CVLT). 35.6% performed below 5th percentile on at least two measures. Dysarthria, functional ratings (despite similar duration), lower education, higher premorbid IQ, and lower ALS motor score related to cognitive impairment.	NOTE: No significant difference between cognitively impaired and intact was found for age, gender, symptom duration, respiratory dysfunction (though difference in score); or depression.							✓
Meier et al. (2010)	18 non-demented ALS & 18 controls	Social cognition (ToM: Faux pas test - social conditions with 50% impairment; emotion recognition: Aprosodia Battery); executive functions (functional decision making: Holiday Apartment Task - most difficult condition only); fluency (letter and category)	Social Cognition (ToM: Faux pas test - control comprehension conditions); Executive (Probabilistic Reversal Learning Test)	✓	✓	✓				

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Montusichi et al. (2015)	183 ALS	12.6% ALS-FTD; 19.7% executive impairment; 5.5% had non-executive cognitive impairment; 6% had behavioural impairment; 6% with non-classifiable cognitive impairment. NOTE: Patients with FTD & those with executive impairment had higher proportion of bulbar onset. ALS-FTD associated with lower education. Survival was lowest for FTD or non-executive impairment (1.9 years and 2 years respectively) compared to behavioural impairment (3 years); cognitively intact (3.1 years) and executive impairment (2.6 years)	No group differences were observed with FVC or ALSFRS-R. However, severity of bulbar symptoms on the ALSFRS-R was lower in ALS-FTD group.							✓
Murphy et al. (2016)	274 sporadic ALS	Possible FTD per cognitive impairment detected in 6.5% of ALS. Non-FTD cognitive impairment found in 54.2%.	Cognitive function not associated with ALSFRS-R or respiratory function, emotional lability, or site of onset.							✓

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Palmieri et al. (2009)	32 ALS, 6 PLS, 1, PBP, 1 PMA, 1 Flail Arm (all without dementia)	Memory (visual: Corsi block tapping)	Memory (digit span forward, prose story); executive functions (working memory: digit span backward; concept formation: WCST; attention/switching: TMT); fluency (letter and category)	✓	✓			✓		
Palmieri et al. (2010)	9 sporadic non-demented ALS & 10 controls	ALS demonstrated no enhancement for remembering unpleasant words compared to controls	Executive functions (Trail Making B-A; digit span backward; WCST); memory (digit span forward; Corsi blocks; word recognition memory test; prose memory test); language (BNT; Token Test); visuospatial (ROCFT); fluency (letter & category)	✓	✓	✓	✓	✓	✓	
Palmieri et al. (2013)	24 non-demented ALS & 27 controls	Fluency (letter and category); numerical calculations	Executive (switching: TMT-A, TMT-B, TMT-A/B; working memory: digit span backward); memory (Prose story, digit span forward); language (BNT)	✓	✓		✓	✓		
Papps et al. (2005)	19 non-demented ALS & 20 controls	Social cognition (Emotion memory i.e., enhancement for emotionally charged material: The Sentence Task)	Social cognition (emotion recognition with Ekman's Faces, ratings of approachability)			✓		✓		

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Pettit et al. (2015)	30 ALS (26 sporadic & 4 familial, 2 C9orf72 positive, 1 FTD)	Memory (immediate and delayed recall and recognition logical memory, digit span forward - WMS); executive functions (working memory: digit span backward divided attention: digit span backward, experimental dual-task paradigm); fluency (letter & spoken)	Language (Graded Naming); visuospatial memory (spatial span forward and backward from WMS); fluency (written); executive (Brixton Spatial Anticipation Test; processing speed (Visual Inspection Time Test; Rapid Serial Letter Identification Task)	✓	✓		✓	✓	✓	
Phukan et al. (2012)	160 ALS & 110 controls	Entire cohort: 28% cognitive impaired, 14% ALS-FTD. Of those with cognitive impairment, differences in executive functioning, language functioning, and memory functioning compared to controls. Executive dysfunction associated with disease progression, older age, lower education and premorbid IQ. Letter fluency was the most sensitive task to executive impairment, with 93.8% of patients with executive dysfunction also demonstrating verbal fluency dysfunction.	The frequency of non-executive cognitive impairment between patients and controls was not significant.							✓

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Pinkhardt et al. (2008)	20 sporadic ALS & 20 controls	Fluency (letter and design); executive functions (selective attention: TAP - incompatibility task).	Executive functions (selective attention/inhibition: Stroop task); fluency (category)	✓	✓					
Raaphorst et al. (2015)	26 non-demented ALS (3 familial) & 21 controls	Memory (Immediate prose recall impaired in 23% RBMT, story recall subtest); executive functions (letter-number sequencing, Stroop - colour naming only); fluency (letter); language (BNT).	Executive (working memory: digit span forward and backward; concept formation: WCST); fluency (category); memory (visual: Doors A and B; verbal: RBMT, 15 words test); visuospatial functioning (JOLO)	✓	✓		✓	✓	✓	
Ringholz et al. (2005)	279 ALS & 129 controls	Cluster analysis showed that 49% of patients and 95% of controls were 'intact', 32% of patients had mild impairment, and 19% had moderate-severe cluster. Errors in tests of attention and working memory accounted for 50% of the variance between groups, with visual recall accounting for 16%, and naming adding 2% to the model. 43 patients held a diagnosis of dementia. Patients with cognitive impairment were more likely to have dysarthria	Site of onset was not significant between groups.							✓

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Savage et al. (2014)	29 ALS (16 with FTD); 25 FTD, & 30 controls	FTD (with or without ALS) showed deficits on social cognition (emotion recognition: Ekman Faces; Awareness of Social Inference Test). Differences on negative emotions anger, disgust, fear, sadness. Sadness (FTD-ALS group only)	ALS without dementia showed no social cognitive deficit on any measure or emotion			✓				
Schmolck et al. (2007)	26 ALS & 40 controls (3 groups including 14 of whom had heart failure)	Patients with ALS rated faces as more approachable than controls. This specifically related to faces that were deemed less approachable than control groups.				✓				
Stukovnik et al. (2010)	22 non-demented ALS & 21 controls	Fluency (letter); executive (planning: Medication Scheduling Task; switching: TMT)	Executive (working memory: Tower of London; inhibition/attention Stroop); fluency (category)	✓	✓			✓		

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
Taylor et al. (2013)	51 ALS & 35 Controls	Composite domains: 31% of patients impaired on executive functions, 43% on language. Executive (D-KEFS sorting; Brixton Spatial Anticipation Test errors); fluency (letter); language (BNT, TROG, KDT; Judgement of Synonyms Subtest from Psycholinguistic Assessment of Language Processing in Aphasia; British Picture Vocabulary Scale; Category Specific Names Test; Spot the Word Test; Graded Difficulty Spelling Test)	Executive functions (D-KEFS description score; Hayling latency score); fluency (category); language (PPT; Oral and Written Naming of Nouns and Verbs errors; Cookie Theft Picture Complexity). NOTE: no relationship between impairment and site of onset.	✓	✓		✓			✓
Tsermentseli et al. (2015)	26 non-demented sporadic ALS (patients with severe bulbar involvement excluded) & 26 controls	Executive functions (Attention: TEA); Language (grammatical comprehension, verb semantics, syntactic complexity and fluency: Cookie Theft picture description task; Token Test, TROG, KDT)	Executive functions (fluency, Hayling Sentence completion latency, WCST); memory (CVLT); visuospatial ability (JOLO, VOSP); language (GNT, British Picture Vocabulary Scale, PPT, Cookie Theft Task: proportions of verbs/nouns)	✓	✓		✓	✓	✓	

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof
van der Hulst et al. (2015)	33 non-demented ALS & 26 controls	Fluency (letter); language (GNT); ToM (judgement of preference). Affective ToM deficit in 12%, cognitive ToM deficit in 3%, 24% with combined dysfunction.	Executive (Brixton Spatial Anticipation); visuospatial (VOSP)	✓	✓	✓	✓		✓	
Volpato et al. (2016)	15 non-demented ALS & 15 controls	Executive functions (set shifting: WCST; selective attention: auditory tone task); memory (object and face recognition: RBMT)	Executive functions (concept formation: WCST); language (verbal comprehension: Aachener Aphasie Test).	✓			✓	✓		
Watermeyer et al. (2015)	55 non-demented ALS & 49 controls	*Composite scores:* Executive functioning, social cognition. Within executive composite: concept formation (D-KEFS); fluency. *Within social cognitive composite:* ToM (Happé Stories Test). NOTE: Executive function predicted social cognition (after controlling for mood and behaviour)	Executive functions (Brixton Spatial Anticipation Test); ToM/emotion recognition (The Awareness of Social Inference Test, Reading the Mind in the Eyes)	✓	✓	✓			✓	
Zalonis et al. (2012)	48 non-demented sporadic ALS & 47 controls	Executive functions (TMT B-A; Stroop; perseverations: WCST; concept formation: similarities of WAIS)	Concept formation (WCST categories); switching (WCST errors). No difference between bulbar and spinal onset.	✓						

				Cognitive Domains Measured						
Article	Population	Impaired	Intact	Exe	Flu	Soc	Lan	Mem	Vis	Prof

✓ = domain is measured in study.

Exec = executive functions, Flu = fluency, Soc = social cognition, Lan = Language functions, Mem = Memory, Vis = Visuospatial Functions, Prof = cognitive profile i.e., proportion of patients impaired and/or profile of impairment.

ACE-R = Addenbrook's Cognitive Examination – Revised; ALSbi = ALS behaviour impairment; ALSci = ALS cognitive impairment; BLOT = Benton Line Orientation Test; BNT = Boston Naming Test; CVLT = California Verbal Learning Test; D-KEFS = Delis-Kaplan Executive Function System; ECAS = Edinburgh Cognitive and Behavioural ALS Screen; FAS = Verbal fluency with letters F, A, and S; FrSBe = Frontal Systems Behaviour Scale; FTD = Frontotemporal Dementia; FVC = Forced Vital Capacity; GNT = Graded Naming Test; JOLO = Judgement of Line Orientation; KOLT = Kendrick Object Learning Test; IGT = Iowa Gambling Test; KDT = Kissing and Dancing Test; PPT = Pyramid and Palm Trees Test

RAVLT = Rey Auditory Verbal Learning Test; RBMT = Rivermead Behavioural Memory Test; RME = Reading the Eyes in the Mind; ROCFT = Rey-Osterrieth Complex Figure Test; SDMT = Symbol Digit Modalities Test; TAP = Testbatterie zur Aufmerksamkeitsprüfung; TEA = Test of Everyday Attention; TMT = Trail-Making Test; ToM = Theory of Mind; TROG = Test for Receptive of Grammar; VFI = Verbal Fluency Index; VOSP = Visual Object and Space Perception Battery; WAIS = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale; WCST = Wisconsin Card Sorting Test.

Appendix II: Supplementary materials for Chapter Two

Supplementary Table 2.1. Description of stimuli development for the ECAS-B and ECAS-C

Language Subtests	
Naming	The original ECAS consists of 8 pictures including both living and non-living things, and manipulable and non-manipulable objects. For each picture in ECAS-A, a selection of alternative objects was chosen that matched the properties of the original pictures. For example, alternative objects for *helicopter* remained as modes of transport such as *tractor* and *caravan*. Alternative stimuli were also matched in terms of word frequency and difficulty based on their reported frequency within the British National Corpus (BNC). Once finalised, all objects were designed and drawn by the University of Edinburgh's graphic department.
Comprehension	As with the ECAS-A, questions were developed using the naming objects as target stimuli. Questions were designed to target 'hidden' features of each object i.e., features that cannot be easily ascertained from the picture alone. As such, the questions maximised the need for a true understanding of what the object is/does. Questions were additionally designed to rely on the understanding of both nouns and verbs for successful completion. Finally, target stimuli were used multiple times to avoid participants using a process of elimination to complete the task.

Language Subtests	
Spelling	The original ECAS spelling words were of low to medium frequency and included nouns, verbs and compound words. Alternative spelling words matched the original words on the same components. Word frequencies were assessed using the BNC. Special attention was paid to the grammatical and orthographical forms of the words to ensure the closest match possible.

Executive Subtests	
Backward digit span	Random samples of numbers were generated using RStudio and the 'sample' function. For example, to generate a random series of 6 numbers the following code was used: > array <- c(1,2,3,4,5,6,7,8,9) > sample(x=array, size = 6, replace = FALSE)
Alternation	No changes were deemed possible in this subtest without fundamentally altering the nature of the task. As such, this subtest was unchanged for the alternate forms.
Sentence completion	Alternate sentences were constructed to include a combination of verbs and nouns, different grammatical structures, and manipulable and non-manipulable objects.

Executive Subtests	
Social cognition	Alternate pictures for this task were not developed to avoid introducing unnecessary confounding elements. Rather, the target item which the face likes is altered for each version. During pilot testing, each participant's own favourite for each box was recording. The face's favourites were chosen to avoid common participant favourites. For example, the item 'bed' is extremely popular among participants and as such, this item was excluded as a possibility for the face's favourite.

Fluency Subtests	
Free fluency	Borkowski, Benton and Spreen (1967) classified letters as hard (Q, J, V, Y, K, U), moderate (I, O, N, E, G, L, R), and easy (H, D, M, W, A, B, F, P, T, C, S). As the letter 'S' from the ECAS-A falls into the Borkowski et al (1967) 'easy' category, selection of alternate letters was restricted to the same category. An additional consideration was those letters incorporated in the most common test of verbal fluency, the COWAT. Letter combinations used in variations of the COWAT are F, A, S (Benton, 1976; Spreen & Benton, 1969); C, F, L and P, R, W (Benton et al., 1994). As such, letters were chosen based on their classification, their presence in the COWAT, and their word frequency (determined using Wordiscope and Litscape).

Fluency Subtests	
Restricted fluency	Like the free fluency task, letters for the restricted fluency were chosen based on their presence in Borkowski et al.'s (1967) 'easy' category. However, unlike the free fluency, greater attention was paid to the letters' word frequency as the COWAT does not include a four-letter restriction condition.

Memory Subtests	
Story recall	Alternative short stories were formulated in the style of a newspaper article with a similar structure and affect. Stories included a name, a job, and two numbers. In total, there were 10 items to be recalled that converted to a total score of immediate recall. It was ensured that the stories did not have a highly emotive storyline that may aid recall.

Visuospatial Subtests	
Dot counting	Alternate dot counting stimuli were developed while retaining the same number of dots, but changing the dots' location. The order of presentation was also retained to enhance equivalence.

Cube counting	Alternate cube counting stimuli were developed while retaining the same number of cubs, but changing the formation of the structures. This is true bar one stimulus. For the ECAS-C, the third structure (which in ECAS-A and ECAS-B has 10 cubes) only has 8 cubes. This is because the 8-cube structure matched most closely in terms of accuracy during piloting.
Number location	The location of the dot and the array of numbers were altered for this task.

References:

Benton, A. L., & Hamsher, S. K. (1978). *Multilingual aphasia examination*. Iowa City, IA: University of Iowa Press

Borkowski, J. G., Benton, A. L., & Spreen, O. (1967). Word fluency and brain damage. *Neuropsychologia*, *5*(2), 135-140.

Spreen, O. & Benton, D. F. (1969). *Neurosensory Center of Comprehensive Examination for Aphasia: Manual of directions*. Victoria, BC: Neuropsychology Laboratory, University of Victoria

Supplementary Table 2.2. Cut-offs for impairment using the ECAS-A-B-C

DOMAIN	SUBTESTS	MAX SCORE	A-B-C
Language	Naming, Comprehension, Spelling	/28	26
Verbal Fluency	Fluency Letter S, Fluency Letter T	/24	14
Executive	Reverse Digit Span, Alternation, Sentence Completion, Social Cognition	/48	33
ALS-SPECIFIC:		**/100**	**77**
Memory	*Immediate recall, Delayed recall score, Delayed recognition*	*/24*	*13*
Visuospatial	*Dot Counting, Cube Counting, Number Location*	*/12*	*10*
ALS NON-SPECIFIC:		***/36***	***24***
ECAS TOTAL SCORE		**/136**	**105**

Supplementary Table 2.3. Practice effects for the ECAS subtests (A-A-A and A-B-C)

	ECAS A-A-A				ECAS A-B-C			
	T1 Mean (SD)	T2 Mean (SD)	T3 Mean (SD)	P-value	T1 Mean (SD)	T2 Mean (SD)	T3 Mean (SD)	P-value
Language†	28.00 (0)	28.00 (0)	28.00 (0)	.283	28.00 (0)	28.00 (0)	28.00 (0)	.524
Fluency	18.70 (4.17)	19.70 (3.33)	20.00 (3.24)	.283	21.05 (2.53)	20.42 (2.06)	20.95 (2.70)	.803
Free	10.10 (1.65)	10.30 (.98)	10.40 (1.05)	.999*	10.53 (1.31)	10.11 (1.24)	10.32 (1.20)	.999
Restricted	8.50 (3.24)	9.40 (2.91)	9.60 (2.56)	.447	10.63 (1.50)	10.32 (1.20)	10.63 (1.77)	.999
Executive	**37.65 (3.76)**	**38.4 (5.27)**	**39.75 (5.09)**	**.030**	41.37 (3.74)	42.05 (3.75)	42.53 (4.53)	.693
Digit Span	**6.4 (1.73)**	**7.2 (1.91)**	**7.6 (1.6)**	**<.001**	7.53 (2.14)	8.00 (2.05)	8.63 (2.34)	.087*§
Sentence Completion	**9.15 (1.63)**	**10.05 (1.32)**	**10.65 (1.42)**	**<.001**	11.05 (1.08)	11.05 (1.08)	11.26 (.65)	.999
Social Cognition†	12.00 (0)	12.00 (0)	12.00 (0)	.999	12.00 (0)	12.00 (0)	12.00 (0)	.999
Memory	**17.90 (2.34)**	**21.65 (2.37)**	**22.40 (1.88)**	**<.001**	19.74 (2.45)	19.47 (1.87)	20.05 (2.20)	.803
Immediate Recall	**6.70 (1.75)**	**8.50 (1.24)**	**9.10 (.91)**	**<.001**	7.63 (1.26)	7.53 (1.54)	7.21 (1.47)	.999
Delayed Recall	9.15 (.81)	9.70 (.66)	9.65 (.81)	.130*§	9.21 (.98)	9.26 (.73)	9.47 (.70)	.999
Recognition	**2.10 (1.12)**	**3.45 (.89)**	**3.65 (.67)**	**<.001***	2.89 (1.10)	2.65 (.95)	3.37 (.68)	.604
ALS Specific	**83.65 (7.32)**	**85.55 (8.36)**	**87.25 (8.21)**	**.007***	89.53 (6.13)	89.95 (5.86)	90.74 (7.35)	.999
ALS Non-Specific	**29.60 (2.46)**	**33.35 (2.46)**	**34.25 (1.80)**	**<.001**	31.58 (2.65)	31.21 (1.99)	31.74 (2.35)	.999
ECAS Total	**113.25 (8.66)**	**118.90 (9.86)**	**121.50 (9.20)**	**<.001**	121.11 (7.53)	121.16 (7.34)	122.47 (9.09)	.999

Note. Due to ceiling effects present in the data, some subtests/domains were not analysed and excluded from the above table. * Greenhouse-Geisser correction applied to p-value. † = Non-parametric Friedman's Test employed, with median and median absolute deviation reported instead of mean and SD. § = p-value significant prior to multiple comparison correction. Holm corrections applied for multiple comparison adjustment for different groups of comparisons (i.e., Group 1=ALS Specific, ALS Non-Specific, ECAS Total = 3 comparisons; Group 2 = Cognitive domains with 4 comparisons, and Group 3 = ECAS subtests with 8 comparisons)

Appendix III: Supplementary materials for Chapter Three

Supplementary Table 3.1. RCI thresholds for the ECAS-A, ECAS-B, and ECAS-C

									ECAS-A to ECAS-B		*ECAS-B to ECAS-C*		*ECAS-A to ECAS-C*	
	$\bar{X}_1$	$\bar{X}_2$	$\bar{X}_3$	S_1	S_2	r_{xx1}	r_{xx2}	r_{xx3}	SE_m	SE_{diff}	SE_m	SE_{diff}	SE_m	SE_{diff}
ALS Specific	85.65	86.39	86.20	8.56	8.55	.87	.91	.90	3.11	4.40	2.77	3.92	2.59	3.66
ALS Non-Specific	30.14	29.89	30.41	3.73	3.66	.85	.88	.86	1.44	2.04	1.37	1.94	1.28	1.81
ECAS Total	115.79	116.28	116.61	115.79	116.28	.90	.94	.93	3.54	5.00	3.09	4.37	2.85	4.04

Note. $\bar{X}_1$ is the mean of ECAS-A, $\bar{X}_2$ is the mean of ECAS-B, $\bar{X}_3$ is the mean of ECAS-C, S_1 is the standard deviation of ECAS-A, S_2 is the standard deviation of ECAS-B, r_{xx1} is the intraclass correlation coefficient of ECAS-A-B, r_{xx2} is the intraclass correlation coefficient of ECAS-B-C, r_{xx3} is the intraclass correlation coefficient of ECAS-A-C, SE_m is the standard error of the measurement, SE_{diff} is the standard error of the difference.

Supplementary Table 3.2. Test-retest reliability of alternate versions of the ECAS

	ECAS-A to ECAS-B			ECAS-A to ECAS-C			ECAS-B to ECAS-C			ECAS-A to ECAS-B to ECAS-C		
	ICC	95% CI	*p*	ICC	95% CI	*p*	ICC	95% CI	*p*	ICC	95% CI	*p*
ALS Specific	.87	.78 - .92	<.0001	.91	.84 - .95	<.0001	.90	.82 - .94	<.0001	.93	.89 - .96	<.0001
Language	.87	.77 - .93	<.0001	.88	.77 - .93	<.0001	.89	.80 - .94	<.0001	.93	.88 - .96	<.0001
Fluency	.73	.54 - .84	<.0001	.80	.65 - .89	<.0001	.79	.63 - .88	<.0001	.84	.75 - .90	<.0001
Executive	.72	.52 - .83	<.0001	.71	.51 - .84	<.0001	.79	.63 - .88	<.0001	.82	.72 - .89	<.0001
ALS Non-Specific	.85	.75 - .91	<.0001	.88	.80 - .93	<.0001	.86	.76 - .92	<.0001	.91	.85 - .94	<.0001
Memory	.86	.77 - .92	<.0001	.87	.77 - .92	<.0001	.87	.77 – 92	<.0001	.91	.85 - .94	<.0001
Visuospatial	.30	-.15 - .58	.082	.31	-.19 - .60	.089	.46	.05 - .69	.02	.47	.16 - .68	.003
ECAS Total	.90	.83 - .94	<.0001	.94	.89 - .96	<.0001	.93	.87 - .96	<.0001	.95	.92 - .97	<.0001

Appendix IV: Supplementary materials for Chapter Four

Table e-1. Patient and Control Cognition and Behaviour

	Controls[a]	ALS[a]	*t* or *W*	*P*-value	*r* or *D*
Cognitive Domains					
ALS Specific	84.26 ± 9.12	76.71 ± 13.44	-5.12	< 0.0001	0.658
Language[b]	28.0 ± 0	27.0 ± 1.48	4614.0	< 0.001	0.237
Executive	38.27 ± 5.89	34.44 ± 7.84	-4.24	< 0.001	0.553
Fluency	19.07 ± 2.95	16.32 ± 5.02	-5.34	< 0.0001	0.668
ALS Non-Specific	29.98 ± 3.76	27.04 ± 5.41	-4.89	< 0.0001	0.629
Memory	18.27 ± 3.43	15.48 ± 4.94	-5.11	< 0.0001	0.657
Visuospatial[b]	12.0 ± 0	12.0 ± 0	5826.0	0.136	-
ECAS Total	114.24 ± 11.65	104.07 ± 16.59	-5.49	< 0.0001	0.709
Behaviour					
ECAS Behaviour[a]		1.0 ± 1.48			
Psychosis (% yes)		6.7			

[a]Values are mean ± one standard deviation. [b]Median ± median absolute deviation are reported. *r* = effect size for Wilcoxon-Mann-Whitney Test, and *D* = Cohen's *D*. *P*-values corrected for multiple comparisons. Behaviour is the number of behavioural dimensions (max 5). Psychosis is defined as the presence one of more of the three measured features.

Table e-2. Tetrachoric correlation coefficients of the cognitive and behavioural features

		ALS Specific			ALS Non-Specific		Behaviour				
		Language	Fluency	Executive	Memory	Visuospatial	Apathy	Disinhibition	Sympathy	Perseveration	Eating
Specific	Language	1									
	Fluency	.46	1								
	Executive	.27	.40	1							
Non-Specific	Memory	.49	.45	.34	1						
	Visuospatial	.33	.13	.36	.08	1					
Behaviour	Apathy	.10	.08	.24	.18	.23	1				
	Disinhibition	.23	.38	.31	.25	.24	.57	1			
	Sympathy	.24	.23	.37	.25	.09	.64	.79	1		
	Perseveration	.12	.22	.28	.17	.44	.53	.37	.46	1	
	Eating	.05	.27	.28	.17	.35	.66	.51	.40	.59	1

Figure e-1. Heatmap of tetrachoric correlations of cognitive and behavioural features

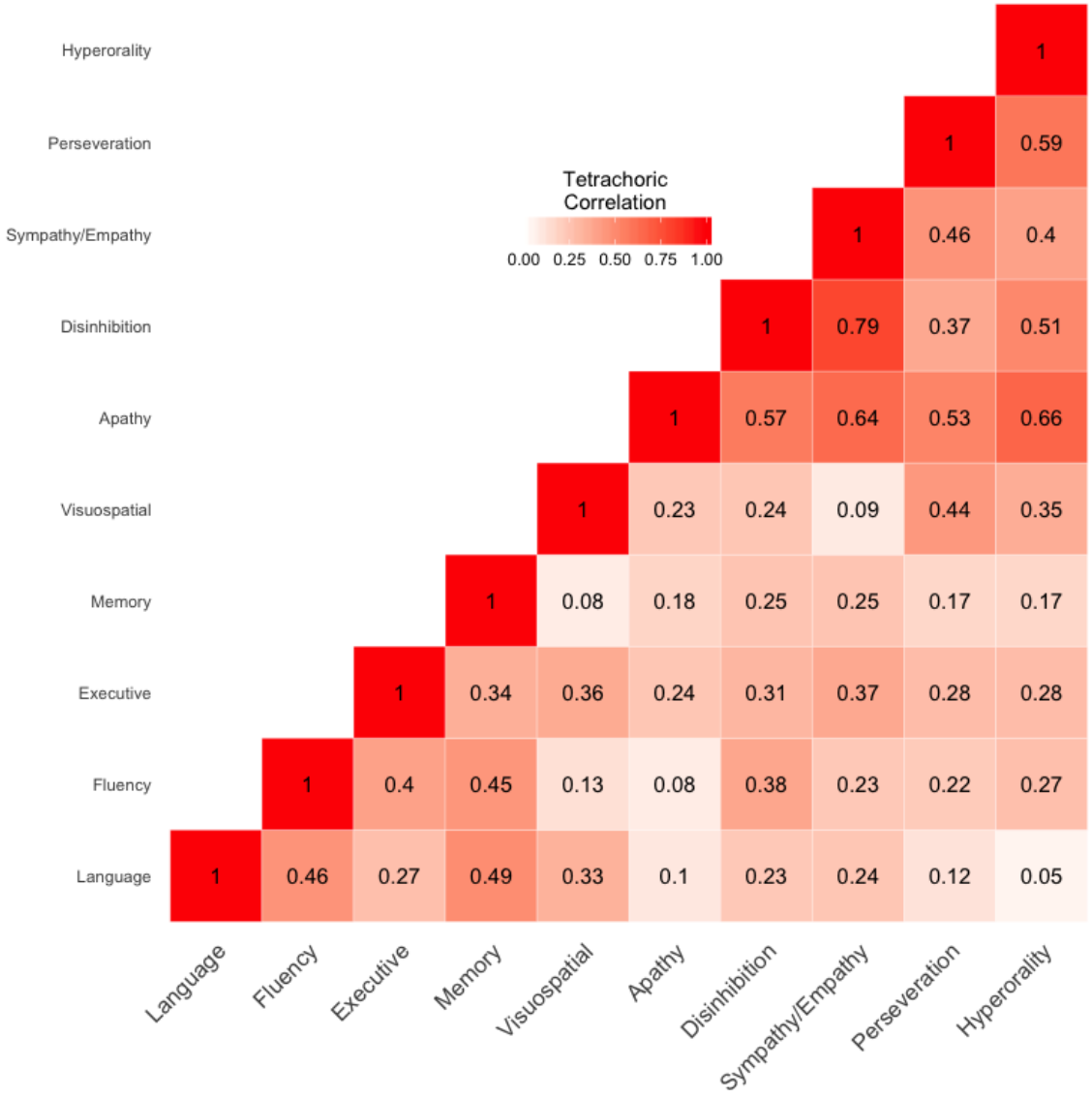


Table e-2. Relationship between cognition, behaviour, and clinical disease variables. (uncorrected)

	ALS Specific	ALS Non-Specific	ECAS Total	Behaviour
Site of onset	F(2,139) = .215, *p* = .807	*F*(2, 140) = .046, *p* = .955	F(2,138) = .241, *p* = .786	*H*(2) = 2.28, *p* = .320
Diagnostic delay	r_s = .078, *p* = .326	r_s = -.018, *p* = .826	r_s = .053, *p* = .520	r_s = -.110, *p* = .182
Riluzole Use	*W* = 2651, *p* = .214	*W* = 2466, *p* = .673	*W* = 2571.5, *p* = .312	*W* = 1989.5, *p* = .871
ALSFRS-R	r_s = .117, *p* = .156	r_s = .041, *p* = .619	r_s = .118, *p* = .156	**r_s = -.258, *p* = .002**
Weight at testing	r_s = .132, *p* = .100	r_s = .084, *p* = .30	r_s = .134, *p* = .097	r_s = -.041, *p* = .626
Bulbar involvement	***W* = 3896.5, *p* = .011**	*W* = 3605.5, *p* = .163	***W* = 3749, *p* = .028**	***W* = 2061, *p* = .005**
Upper limb involvement	*W* = 2679, *p* = .567	*W* = 2395, *p* = .465	*W* = 2608.5, *p* = .698	*W* = 2040, *p* = .527
Lower limb involvement	*W* = 2142, *p* = .136	*W* = 2337, *p* = .411	*W* = 2112, *p* = .125	*W* = 2036, *p* = .621
HADS-D	**r_s = -.169 , *p* = .041**	r_s = -.096 , *p* = .248	**r_s = -.168, *p* = .043**	**r_s = .360, *p* < .001**
HADS-A	r_s = -.084 , *p* = .312	r_s = -.040, *p* = .633	r_s = -.093, *p* = .264	**r_s = .20 *p* = .019**

Note. Site of onset compared bulbar, upper limb, and lower limb. HADS-D = Hospital Anxiety and Depression Scale (Depression Score). HADS-A = Hospital Anxiety and Depression Scale (Anxiety Score); F = one-way ANOVA; H = Kruskal-Wallis rank sums test; r_s = Spearman correlation.

The above table contains scores uncorrected for multiple comparisons. Holm-Bonferroni corrections were applied for each clinical variable and displayed in Supplementary Table 3.

Table e-3. Relationship between cognition, behaviour, and clinical disease variables (corrected)

	ALS Specific	ALS Non-Specific	ECAS Total	Behaviour
ALSFRS-R	r_s = .117, *p* = .469	r_s = .041, *p* = .619	r_s = .118, *p* = .469	**r_s = -.258, *p* = .009**
Bulbar involvement	***W* = 3896.5, *p* = .033**	*W* = 3605.5, *p* = .163	*W* = 3749, *p* = .057	***W* = 2061, *p* = .019**
HADS-D	r_s = -.169 , *p* = .122	r_s = -.096 , *p* = .248	r_s = -.168, *p* = .122	**r_s = .360, *p* < .001**
HADS-A	r_s = -.084 , *p* = .792	r_s = -.040, *p* = . 792	r_s = -.093, *p* = . 792	r_s = .20 *p* = .075

Note. HADS-D = Hospital Anxiety and Depression Scale (Depression Score). HADS-A = Hospital Anxiety and Depression Scale (Anxiety Score); r_s = Spearman correlation.

Table e-4. Cognitive and behavioural data across King's disease stages by bulbar involvement

	Stage 1	Stage 2	Stage 3	Stage 4
Bulbar Yes				
N	15	11	22	35
ALS Specific	76.33 ± 17.17	81.09 ± 7.45	74.76 ± 15.12	69.46 ± 15.88
ALS Non-Specific	25.60 ± 8.30	29.36 ± 3.44	27.73 ± 4.41	24.62 ± 6.55
ECAS Total	101.93 ± 24.95	110.45 ± 7.95	102.24 ± 18.47	95.59 ± 18.34
Behaviour*	0 ± 0	0 ± 0	1 ± 1.48	2.5 ± 1.48
Bulbar No				
N	25	34	0	19
ALS Specific	79.29 ± 10.51	80.65 ± 10.50	-	79.68 ± 9.28
ALS Non-Specific	27.84 ± 4.22	27.56 ± 4.07	-	28.42 ± 4.80
ECAS Total	107.04 ± 12.10	108.21 ± 13.19	-	108.11 ± 12.21
Behaviour*	0 ± 0	0 ± 0	-	0.5 ± 0.74

Note. * median and median absolute deviation. Stage 3 is defined as the presence of upper limb, lower limb, an bulbar symptoms, and as such, there are no patients in Stage 3 without bulbar involvement.

Appendix V: ECAS A-B-C: Forms and guidelines

EDINBURGH COGNITIVE AND BEHAVIOURAL ALS SCREEN – ECAS
English Version A (2013)

Date of testing: .....
Age at leaving full-time education: .....
Occupation: .....
.....
Handedness: .....

Name: .....
Date of Birth: .....
Hospital No. or Address: .....
.....
.....

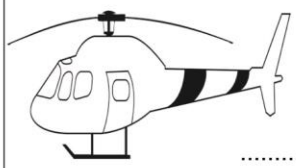
LANGUAGE - Naming

➲ Ask: Say or write down the names of these pictures:

Score 0-8 ☐


.....


.....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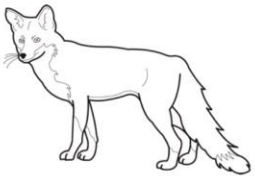
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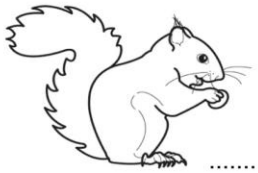
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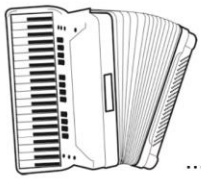
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LANGUAGE - Comprehension

➲ Ask: point to the one which is:

Score 0-8 ☐

1. Something you can fly in .....
2. Something with webbed feet .....
3. An animal that climbs trees .....
4. Something used for chopping .....
5. A means of transport .....
6. Something with a sharp edge .....
7. Something with a sting .....
8. Something with a diet of nuts and seeds .....

MEMORY – Immediate recall

Score 0-10 ☐

Also use this score to calculate % retention later

➲ Say: 'I am going to read you a short story. Please listen carefully. When I am finished, say or write as much as you can remember'. Score 1 point for each (either entire or part of) underlined section recalled.

Last Sunday, the annual litter collection took place in Primrose Woods. Forty two people joined in to remove old bicycles and shopping trolleys. Mr Douglas Watt from the woodland project told local reporters that he was very impressed and especially proud of the 17 children who came along.

LANGUAGE - Spelling

Score 0-12 ☐

➲ Say: 'Spell, either by writing or speaking, the following words.' If the person is using assistive technology, ask them to turn off any predictive text facility.

1. Envelope	2. Skateboard .....
3. Constructing	4. Partner .....
5. Biscuit	6. Lawnmower .....
7. Deliver	8. Recorded .....
9. Coathanger	10. Orchestra .....
11. Screwdriver	12. Brought .....

FLUENCY - Letter S

No. of correct words =

Time to copy/ read aloud =

➲ Say: 'I am going to give you a letter of the alphabet and I would like you to say or write as many different words as you can beginning with that letter, but not names of people or places, or numbers.'
- If writing, say: 'You will have **two** minutes. The letter is S.'
- If speaking, say 'You will have **one** minute. The letter is S.'

➲ Next the person copies/reads these words aloud.

- If writing, say: 'copy these words as fast as possible. I will time you. Ready? Begin.'

If speaking, say: 'read aloud these words as fast as possible. Before you do this, check that you can read them. I will time you. Ready? Begin.'

Verbal Fluency Index (Vfi) calculation:

If spoken:

$$Vfi = \frac{60 \text{seconds} - \text{no. of seconds to read aloud words}}{\text{No. of correct words generated}}$$

If written:

$$Vfi = \frac{120 \text{seconds} - \text{no. of seconds to copy words}}{\text{No. of correct words generated}}$$

VFI conversion to score table

SPOKEN VFI	WRITTEN VFI	Score
≥ 12.00	≥ 20.00	**0**
10.00 to <12.00	16.50 to < 20.00	**2**
8.00 to < 10.00	13.00 to < 16.50	**4**
6.00 to < 8.00	9.50 to < 13.00	**6**
4.00 to < 6.00	6.00 to < 9.50	**8**
2.00 to < 4.00	2.50 to < 6.00	**10**
< 2.00	< 2.50	**12**

Score 0-12 ☐

EXECUTIVE – Reverse Digit Span

➲ Say: 'I am going to say some numbers and I would like you to say them back to me in reverse order. For example, if I say '2 3 4', you should say '4 3 2'. Let's have a practice. If I say '7 1 9', what would you say?' Stop when person gets both trials of a line wrong. Score total number of trials correct.

Score 0-12 ☐

Trial		Check	Trial		Check
1	2 6		**2**	5 8	
3	9 3 5		**4**	4 1 6	
5	7 2 8 4		**6**	9 5 7 3	
7	6 9 4 2 1		**8**	8 3 2 5 6	
9	8 1 3 5 7 9		**10**	3 6 2 7 3 4	
11	1 6 9 3 5 8 6		**12**	2 3 6 8 4 9 2	

EXECUTIVE – Alternation

➲ Say: 'I want you to alternate between numbers and letters, starting with 1-A, then 2-B, 3-C, and so on. Please alternate between numbers and letters, in order, without skipping any until I tell you to stop'. 'Let's begin together: 1-A, 2-B, 3-C'.

Score 0-12 ☐

Trial		Check	Trial		Check	Trial		Check	Trial		Check
1	4-D		**2**	5-E		**3**	6-F		**4**	7-G	
5	8-H		**6**	9-I		**7**	10-J		**8**	11-K	
9	12-L		**10**	13-M		**11**	14-N		**12**	15-O	

FLUENCY - Letter T

➲ Say: 'I am going to give you a letter of the alphabet and I would like you to say or write as many different words as you can beginning with that letter, but not names of people or places, or numbers. This time the word must only be four letters long. No more or less than four letters'

- If writing, say: 'You will have **two** minutes. The letter is T.'
- If speaking, say 'You will have **one** minute. The letter is T.'

No. of correct words =

Time to copy/ read aloud =

➲ Next the person copies/reads these words aloud.

- If writing, say: 'copy these words as fast as possible. I will time you. Ready? Begin.'

If speaking, say: 'read aloud these words as fast as possible. Before you do this, check that you can read them. I will time you. Ready? Begin.'

Verbal Fluency Index (Vfi) calculation:

If spoken:

$$Vfi = \frac{60\text{seconds} - \text{no. of seconds to read aloud words}}{\text{No. of correct words generated}}$$

If written:

$$Vfi = \frac{120\text{seconds} - \text{no. of seconds to copy words}}{\text{No. of correct words generated}}$$

VFI conversion to score table

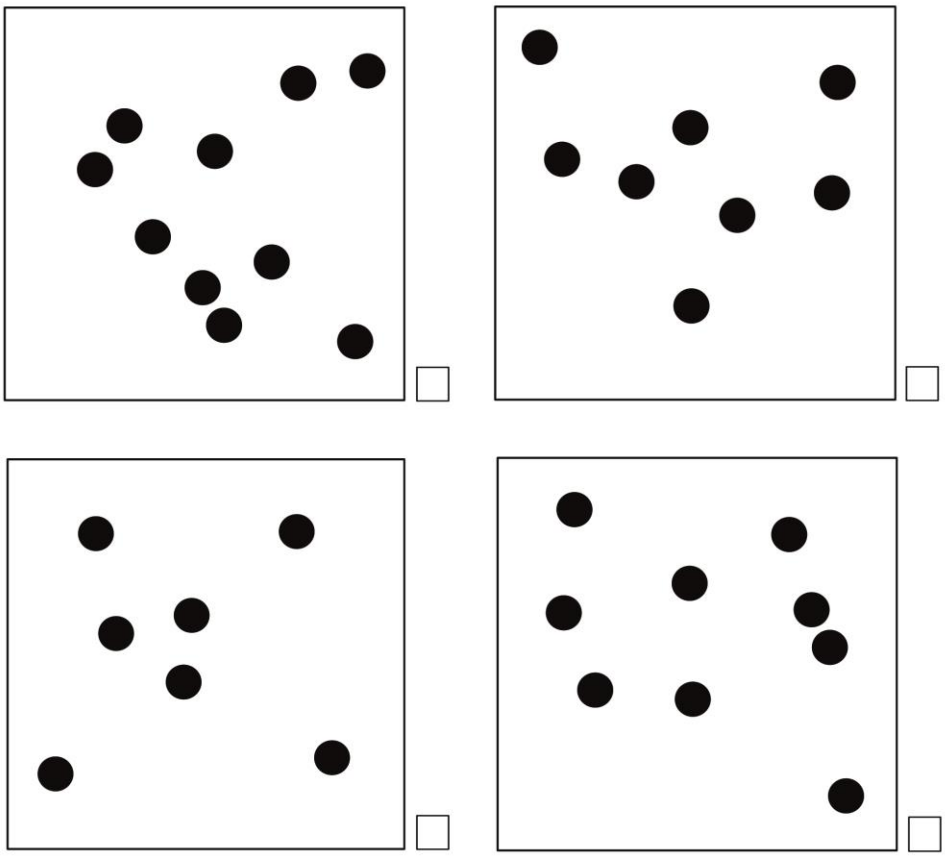
SPOKEN VFI	WRITTEN VFI	Score
≥ 20.00	≥ 27.25	**0**
16.75 to < 20.00	23.00 to < 27.25	**2**
13.50 to < 16.75	18.75 to < 23.00	**4**
10.25 to < 13.50	14.50 to < 18.75	**6**
7.00 to < 10.25	10.25 to < 14.50	**8**
3.75 to < 7.00	6.00 to < 10.25	**10**
< 3.75	< 6.00	**12**

Score 0-12 ☐

VISUOSPATIAL – Dot Counting

➲ Say: 'I would like you to count how many dots are in each box, but without pointing to them.'

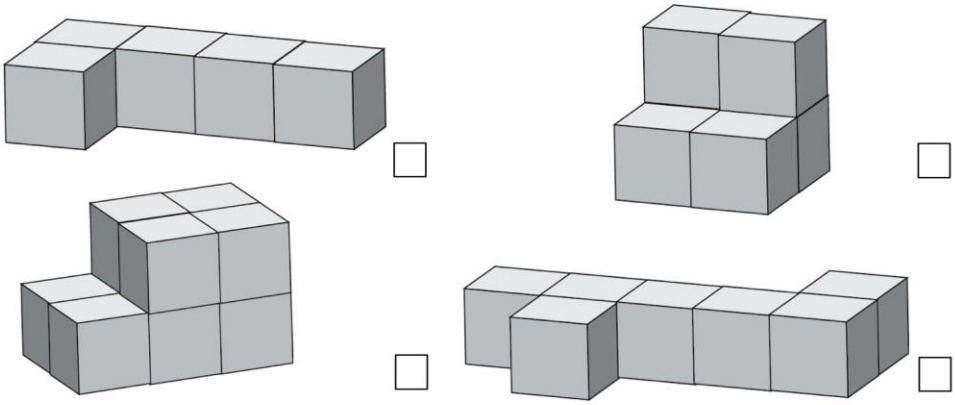
Score
0-4



VISUOSPATIAL – Cube Counting

➲ Say: 'How many cubes are in each structure, including the ones you may not be able to see?'

Score
0-4

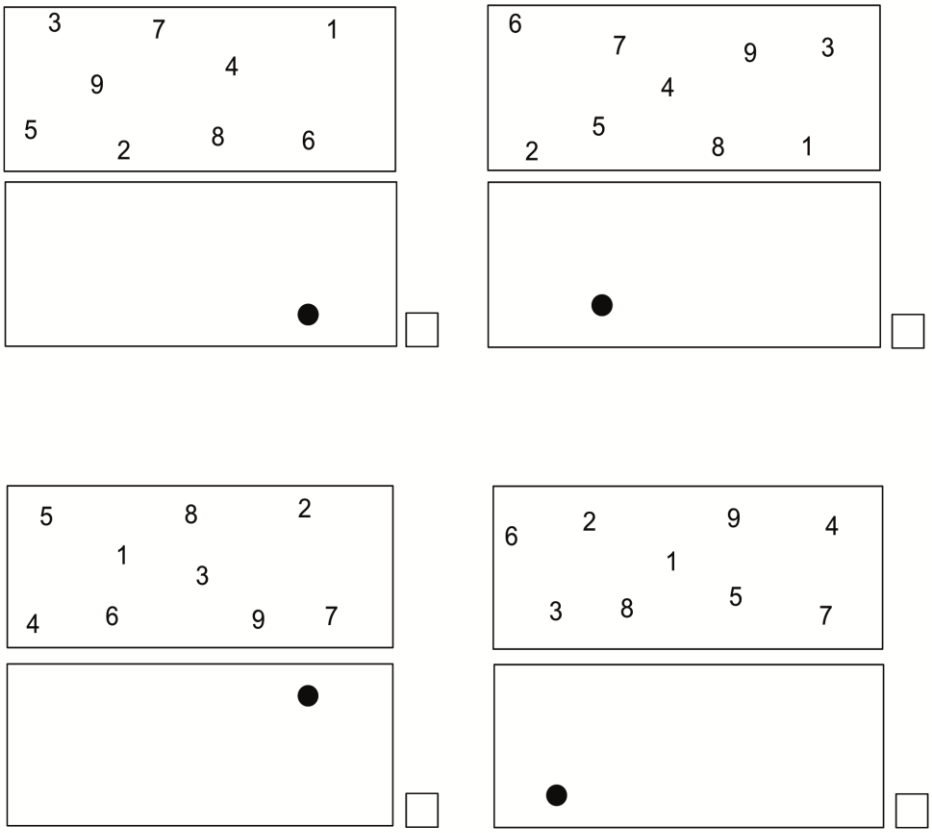


S. Abrahams & T. H. Bak 4

VISUOSPATIAL – Number Location

➲ Say: 'Which number corresponds to the position of the dot?'

Score 0-4 ☐



EXECUTIVE – Sentence Completion

➲ Say: 'Listen carefully to these sentences and as soon as I have finished reading them, please tell me, or write, a word that finishes the sentence as quickly as possible. For example, '*She was so tired that she went straight to…bed*'. Do not score.

1. He phoned up the restaurant to reserve a .....
2. When she got up in the morning, the sun was.....

➲ Say: 'Now I'd like you to do that again, but this time the word you give should not make sense whatsoever in the context of the sentence. It must not be related to the word that actually completes the sentence. For example, '*John cut his hand with the sharp…orange*'. If the person does not respond within 20 seconds, move onto the next question.

1. The postman knocked on the .....

2. He brought his umbrella with him in case of .....

3. Sally spread her toast with butter and .....

4. John went to the barbers to get his hair .....

5. She dived into the swimming .....

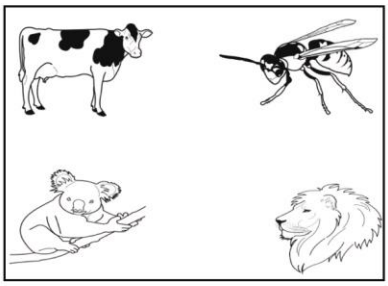
6. They all went to the local café for something to .....

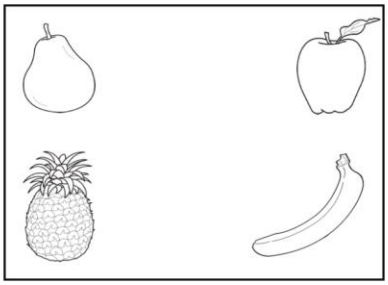
Give 2 points for different word, 1 point for related word (e.g. associated or opposite meaning) or 0 points for exact word.

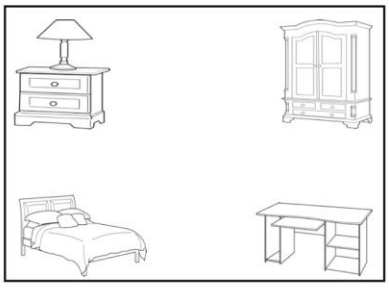
Score 0-12 ☐

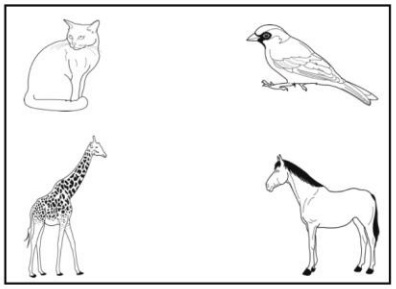
SOCIAL COGNITION – Part A

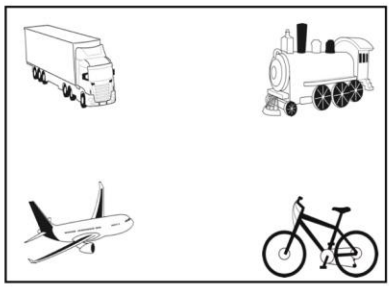
➲ Say: 'You are going to see some pictures, one in each corner of a box. You have to choose **which picture you like best.** Either point to or say which picture you like best. Please respond as quickly as possible.' Circle participant's choice.







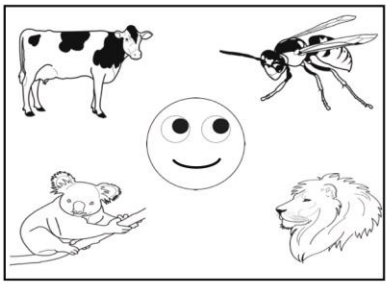


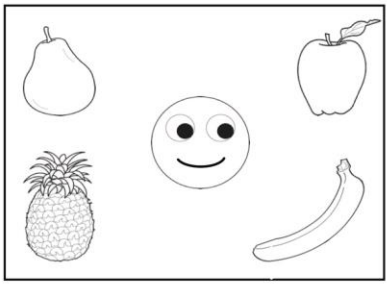


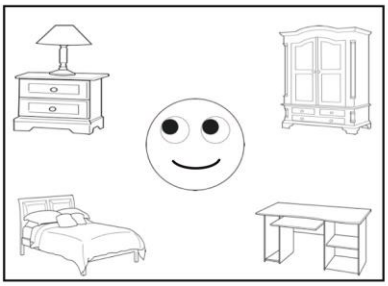
SOCIAL COGNITION – Part B

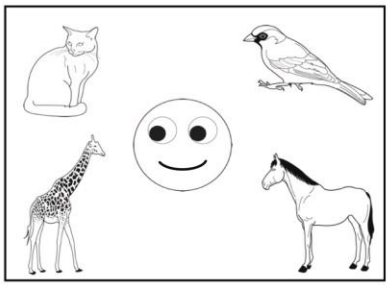
➲ Say: 'You are going to see some pictures, one in each corner of a box. You have to choose **which picture does the face like best.** Either point to or say which picture **the face likes best**. Please respond as quickly as possible.' Circle participant's choice. Correct items = 2 points, error = 1 point, egocentric error = 0 points.

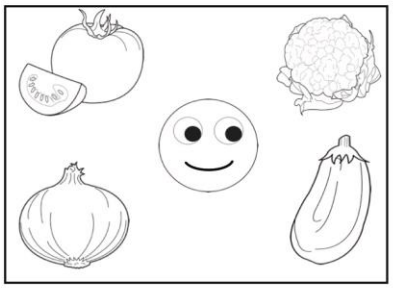
Score 0-12

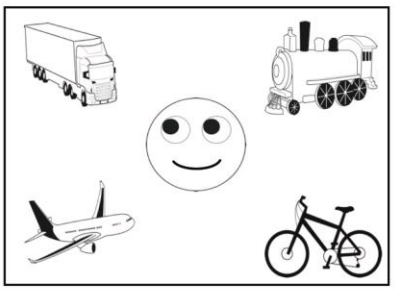












MEMORY – Delayed Recall

Scoring procedure for retention: obtain delayed recall performance (over page) and, together with immediate recall score, determine percentage retained. Convert percentage retained to Score using table below. If delayed recall = 0, score = 0.

Delayed recall to percentage retained calculation	Percentage retained to score conversion table

$$\frac{\text{(Delayed recall)}}{\text{(Immediate recall score)}} \quad x\ 100 = \%\ \text{retained}$$

$$\frac{(\ldots\ldots\ldots\ldots\ldots\ldots)}{(\ldots\ldots\ldots\ldots\ldots\ldots)} \quad x\ 100 = \ldots\ldots\ldots\ldots\%\ \text{retained}$$

Percentage retained	**Score**	Percentage retained	**Score**
1-10%	**1**	51-60%	**6**
11-20%	**2**	61-70%	**7**
21-30%	**3**	71-80%	**8**
31-40%	**4**	81-90%	**9**
41-50%	**5**	91-100+ %	**10**

➲ Say: 'At the beginning of this interview, I read you a short story. Tell me as much as you can remember from that story'. Mark 1 point for each (either entire or part of) underlined section recalled.

Last Sunday, the annual litter collection took place in Primrose Woods. Forty two people joined in to remove old bicycles and shopping trolleys. Mr Douglas Watt from the woodland project told local reporters that he was very impressed and especially proud of the 17 children who came along.

Delayed recall =

Score (0-10) ☐

MEMORY – Delayed Recognition

If all items recalled, skip and score 4. Otherwise ask questions below.

Say: 'Lets see if you can remember anything more about that story. I will ask you some questions, please tell me if they are true or false'.

Circle responses (true or false) and mark 1 point for each item recognised in this section. Use table below to calculate score.

Score 0-4 ☐

Was the story about an event that occurred last Saturday?	T	**F**	1
Was the event the annual litter collection?	**T**	F	1
Did this take place in Primrose Woods?	**T**	F	1
Did they remove old drink cans and sweet wrappers?	T	**F**	1
Was the man in the story called Mr Watt?	**T**	F	1
Was his first name 'Thomas'?	T	**F**	1
Was he from the local council?	T	**F**	1
Was he especially proud of the children for coming along?	**T**	F	1

Recognition to recognition score table	
Number of correct answers	**Score**
0-4	**0**
5	**1**
6	**2**
7	**3**
8	**4**

SCORES

Language	Naming, Comprehension, Spelling	/28
Verbal Fluency	Fluency Letter S, Fluency Letter T	/24
Executive	Reverse Digit Span, Alternation, Sentence Completion, Social Cognition	/48
	ALS-SPECIFIC:	**/100**
Memory	*Immediate recall, Delayed recall score, Delayed recognition*	*/24*
Visuospatial	*Dot Counting, Cube Counting, Number Location*	*/12*
	ALS NON-SPECIFIC:	***/36***
	ECAS TOTAL SCORE:	**/136**

EDINBURGH COGNITIVE and BEHAVIOURAL ALS SCREEN – ECAS
English Version (2013)

BEHAVIOUR SCREEN – Carer Interview

➲ Please ask the carer about the following possible behaviours. Symptoms should have occurred repeatedly and not just on one instance, and may have occurred prior to the development of any motor signs. Tick 'Yes', 'No' or 'Don't Know'. If 'Yes', please provide a brief written description. Give one mark for every 'Yes' response (maximum = 10).

A	**Behavioural disinhibition**			
1	Socially inappropriate behaviour, e.g. *inappropriate behaviour with strangers* *criminal behaviour*	Y	N	DK
2	Loss of manners or decorum, e.g. *crude or sexually explicit remarks, jokes or opinions that may be offensive to others* *lack of response to social cues*	Y	N	DK
3	Impulsive, rash or careless actions, e.g. *new onset gambling, or buying or selling property without regard for consequences* *giving out personal information inappropriately, e.g. credit card numbers*	Y	N	DK
B	**Apathy or inertia**			
4	Loss of interest, drive or motivation, e.g. *passivity and lack of spontaneity* *needs prompting to initiate or continue routine activities*	Y	N	DK
C	**Loss of sympathy or empathy**			
5	Diminished response to other people's needs and feelings *Positive rating on this feature should be based on specific examples that reflect a lack of understanding or indifference to other people's feelings, e.g* *hurtful comments* *disregard for others' pain or distress*	Y	N	DK
6	Diminished social interest, interrelatedness, personal warmth or general closeness in social engagement, e.g. *coldness* *lack of eye contact*	Y	N	DK
D	**Perseverative, stereotyped, compulsive or ritualistic behaviour**			
7	Simple repetitive movements, e.g. *tapping, clapping* *scratching, picking skin or clothing* *repeating words*	Y	N	DK
8	Complex, compulsive or ritualistic behaviours, e.g. *counting, cleaning rituals, checking* *collecting, hoarding*	Y	N	DK

BEHAVIOUR

E	**Hyperorality and altered food preferences**				
9	Altered food preferences, e.g. *food fads* *carbohydrate craving (particularly sweets)*	Y	N	DK	
10	Binge eating or hyperorality, e.g., *cramming or continuing to eat despite satiety* *oral exploration or consumption of inedible objects*	Y	N	DK	
SCORE					
	TOTAL				***/10***

SYMPTOMS	
➲ Please tick box if at least one of the symptoms was present in each of the following categories.	
A. Behavioural disinhibition	
B. Apathy or inertia	
C. Loss of sympathy or empathy	
D. Perseverative, stereotyped, compulsive or ritualistic behaviour	
E. Hyperorality and altered food preferences	

ALS Psychosis Screen

➲ Please ask the carer about the following possible symptoms. Tick 'Yes', 'No' or 'Don't Know'. If 'Yes', please provide a brief written description. Give one mark for every 'Yes' response (maximum = 3).

1	Has strange and/or bizarre beliefs and behaviours	Y	N	DK
2	Hears or sees things that are not there, and/or feels the presence of someone who is not there	Y	N	DK
3	Is overly suspicious, and/or feels persecuted	Y	N	DK
SCORE				
	TOTAL			***/3***

ONSET AND DURATION OF SYMPTOMS		
➲ Please tick or complete box to indicate response.		
1. Do these symptoms represent a CHANGE from the patient's previous behaviour?	Y	N
If yes, did the changes occur:		
a. BEFORE the onset of the disease?	Y	N
b. at the same time as other symptoms?	Y	N
c. AFTER the onset of the disease?	Y	N
2. Do they still persist?	Y	N
3. If not, how long did they last?		

EDINBURGH COGNITIVE AND BEHAVIOURAL ALS SCREEN – ECAS
English Version B (2017)

Date of testing: .....
Age at leaving full-time education: .....
Occupation: .....
.....
Handedness: .....

Name: .....
Date of Birth: .....
Hospital No. or Address: .....
.....
.....

LANGUAGE - Naming

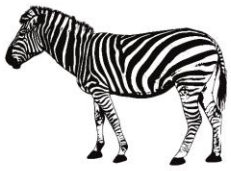
➲ Ask: Say or write down the names of these pictures:

Score 0-8 ☐


.....☐


.....☐


.....☐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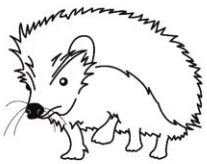
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LANGUAGE - Comprehension

➲ Ask: point to the one which is:

Score 0-8 ☐

1. Something you wear…….....
2. An animal with colourful feathers…….....
3. Something you play…….....
4. A means of transport……..….....
5. Something a plumber might use.....
6. Something that rolls into a ball.....
7. Something used on a farm.....
8. Something that lives in the African savannah…….....

MEMORY – Immediate recall

Score 0-10 ☐

Also use this score to calculate % retention later

➲ Say: 'I am going to read you a short story. Please listen carefully. When I am finished, say or write as much as you can remember'. Score 1 point for each (either entire or part of) underlined section recalled.

Three fishing boats helped rescue a whale that swam too close to the shore. The whale was spotted swimming in circles. Alan Williams from the Marine Conservation Trust said thirty-two young whales got lost last winter when looking for food.

LANGUAGE - Spelling

Score 0-12 ☐

➲ Say: 'Spell, either by writing or speaking, the following words.' If the person is using assistive technology, ask them to turn off any predictive text facility.

1. Lecture	.....	2. Toothpick	.....
3. Gathering	.....	4. Pollution	.....
5. Receipt	.....	6. Sunflower	.....
7. Inspire	.....	8. Argued	.....
9. Watermelon	.....	10. Dictionary	.....
11. Earthquake	.....	12. Thought	.....

FLUENCY - Letter F

No. of correct words =

Time to copy/ read aloud =

➲ Say: 'I am going to give you a letter of the alphabet and I would like you to say or write as many different words as you can beginning with that letter, but not names of people or places, or numbers.'
- If writing, say: 'You will have **two** minutes. The letter is F.'
- If speaking, say 'You will have **one** minute. The letter is F.'

➲ Next the person copies/reads these words aloud.

- If writing, say: 'copy these words as fast as possible. I will time you. Ready? Begin.'

If speaking, say: 'read aloud these words as fast as possible. Before you do this, check that you can read them. I will time you. Ready? Begin.'

Verbal Fluency Index (Vfi) calculation:

If spoken:

$$Vfi = \frac{60 \text{ seconds} - \text{no. of seconds to read aloud words}}{\text{No. of correct words generated}}$$

If written:

$$Vfi = \frac{120 \text{ seconds} - \text{no. of seconds to copy words}}{\text{No. of correct words generated}}$$

VFI conversion to score table

SPOKEN VFI	WRITTEN VFI	Score
≥ 12.00	≥ 20.00	**0**
10.00 to < 12.00	16.50 to < 20.00	**2**
8.00 to < 10.00	13.00 to < 16.50	**4**
6.00 to < 8.00	9.50 to < 13.00	**6**
4.00 to < 6.00	6.00 to < 9.50	**8**
2.00 to < 4.00	2.50 to < 6.00	**10**
< 2.00	< 2.50	**12**

Score 0-12 ☐

EXECUTIVE – Reverse Digit Span

➲ Say: 'I am going to say some numbers and I would like you to say them back to me in reverse order. For example, if I say '2 3 4', you should say '4 3 2'. Let's have a practice. If I say '7 1 9', what would you say?' Stop when person gets both trials of a line wrong. Score total number of trials correct.

Score 0-12 ☐

Trial		Check	Trial		Check
1	2 8		**2**	4 9	
3	5 1 3		**4**	8 2 4	
5	1 5 2 7		**6**	6 3 8 1	
7	9 4 3 8 6		**8**	2 4 1 9 7	
9	1 8 3 5 4 2		**10**	7 3 9 2 6 1	
11	4 8 2 6 8 3 1		**12**	5 1 6 4 2 9 3	

EXECUTIVE – Alternation

➲ Say: 'I want you to alternate between numbers and letters, starting with 1-A, then 2-B, 3-C, and so on. Please alternate between numbers and letters, in order, without skipping any until I tell you to stop. Let's begin together: 1-A, 2-B, 3-C.'

Score 0-12 ☐

Trial		Check	Trial		Check	Trial		Check	Trial		Check
1	4-D		**2**	5-E		**3**	6-F		**4**	7-G	
5	8-H		**6**	9-I		**7**	10-J		**8**	11-K	
9	12-L		**10**	13-M		**11**	14-N		**12**	15-O	

FLUENCY - Letter D

➲ Say: 'I am going to give you a letter of the alphabet and I would like you to say or write as many different words as you can beginning with that letter, but not names of people or places, or numbers. This time the word must only be four letters long. No more or less than four letters'

- If writing, say: 'You will have **two** minutes. The letter is D.'
- If speaking, say 'You will have **one** minute. The letter is D.'

No. of correct words =

Time to copy/ read aloud =

➲ Next the person copies/reads these words aloud.

- If writing, say: 'copy these words as fast as possible. I will time you. Ready? Begin.'

If speaking, say: 'read aloud these words as fast as possible. Before you do this, check that you can read them. I will time you. Ready? Begin.'

Verbal Fluency Index (Vfi) calculation:

If spoken:

$$Vfi = \frac{60\text{seconds} - \text{no. of seconds to read aloud words}}{\text{No. of correct words generated}}$$

If written:

$$Vfi = \frac{120\text{seconds} - \text{no. of seconds to copy words}}{\text{No. of correct words generated}}$$

VFI conversion to score table

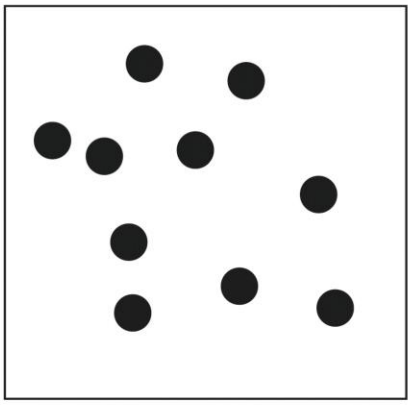
SPOKEN VFI	WRITTEN VFI	Score
≥ 20.00	≥ 35.00	**0**
16.75 to < 20.00	28.50 to < 35.00	**2**
13.50 to < 16.75	22.00 to < 28.50	**4**
10.25 to < 13.50	15.50 to < 22.00	**6**
7.00 to < 10.25	9.00 to < 15.50	**8**
3.75 to < 7.00	2.50 to < 9.00	**10**
< 3.75	< 2.50	**12**

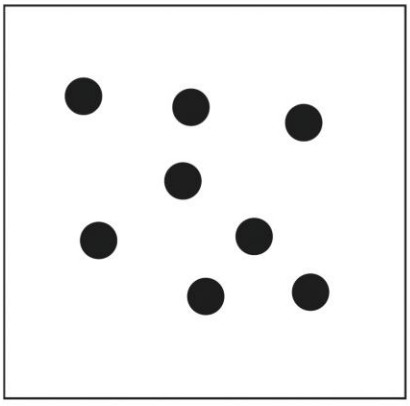
Score 0-12 ☐

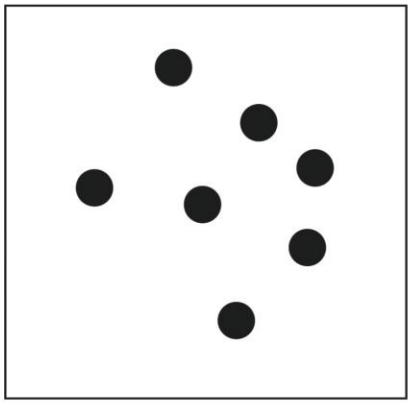
VISUOSPATIAL – Dot Counting

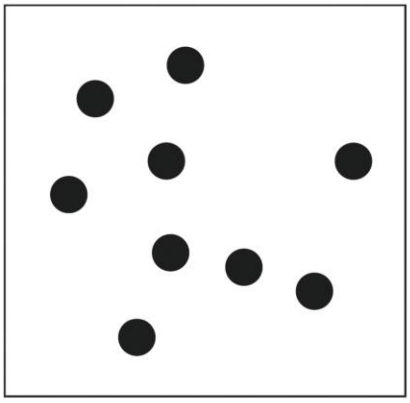
➲ Say: 'I would like you to count how many dots are in each box, but without pointing to them.'

Score
0-4





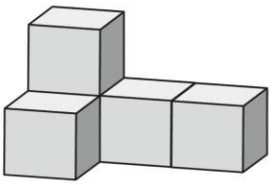


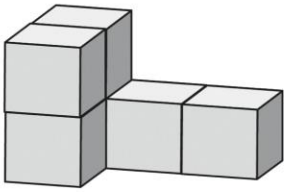


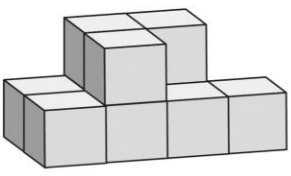
VISUOSPATIAL – Cube Counting

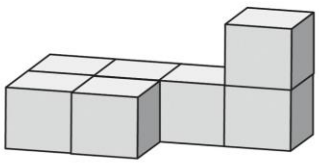
➲ Say: 'How many cubes are in each structure, including the ones you may not be able to see?'

Score
0-4





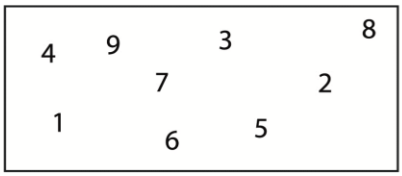


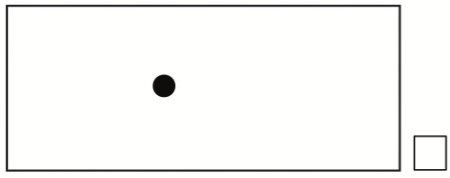


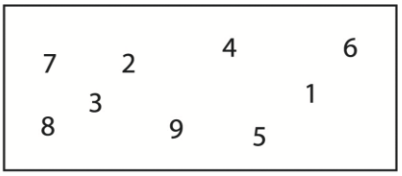
VISUOSPATIAL – Number Location

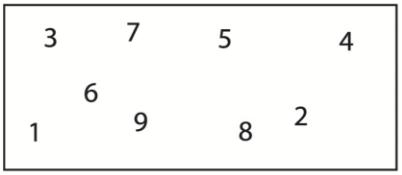
➲ Say: 'Which number corresponds to the position of the dot?'

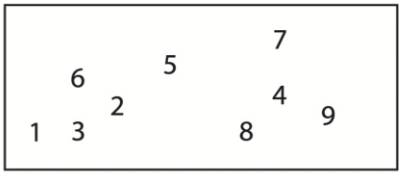
Score 0-4 ☐











EXECUTIVE – Sentence Completion

➲ Say: 'Listen carefully to these sentences and as soon as I have finished reading them, please tell me, or write, a word that finishes the sentence as quickly as possible. For example, '*She was so tired that she went straight to…bed*'. Do not score.

1. He phoned up the restaurant to reserve a .....
2. When she got up in the morning, the sun was.....

➲ Say: 'Now I'd like you to do that again, but this time the word you give should not make sense whatsoever in the context of the sentence. It must not be related to the word that actually completes the sentence. For example, '*John cut his hand with the sharp…orange*'. If the person does not respond within 20 seconds, move onto the next question.

1. She answered the phone because it was .....

2. The joke was so funny, he started to .....

3. Daniel unlocked the door with a .....

4. The child cut paper with a pair of .....

5. After months of practice, Lisa passed her driving .....

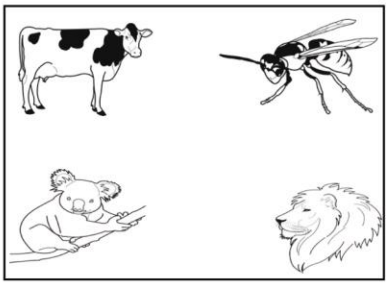
6. Simon ate his dinner with a knife and .....

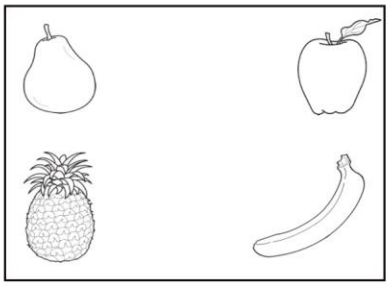
Give 2 points for different word, 1 point for related word (e.g. associated or opposite meaning) or 0 points for exact word.

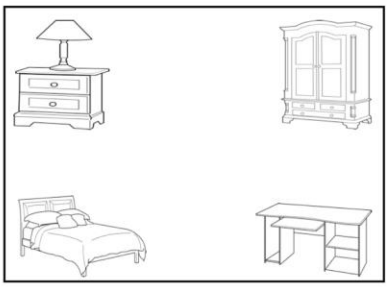
Score 0-12 ☐

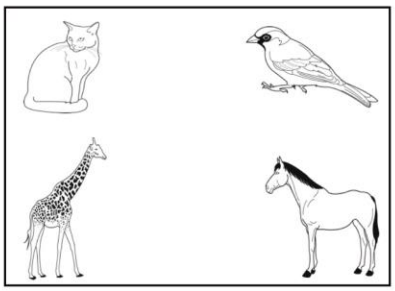
SOCIAL COGNITION – Part A

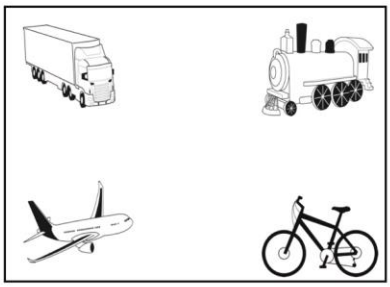
➲ Say: 'You are going to see some pictures, one in each corner of a box. You have to choose **which picture you like best.** Either point to or say which picture you like best. Please respond as quickly as possible.' Circle participant's choice.







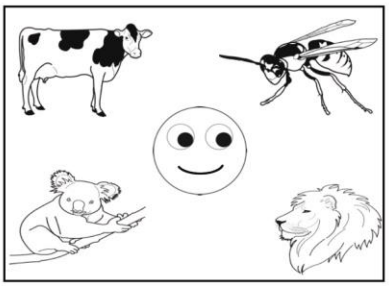


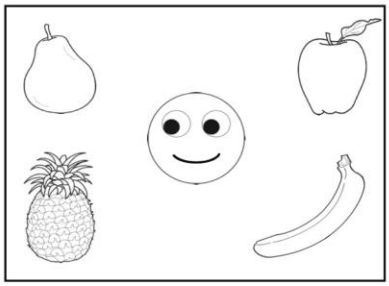


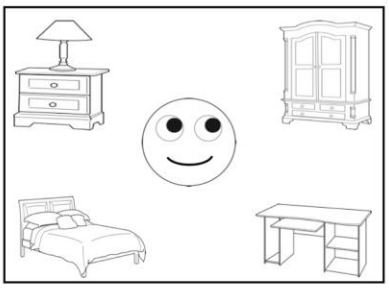
SOCIAL COGNITION – Part B

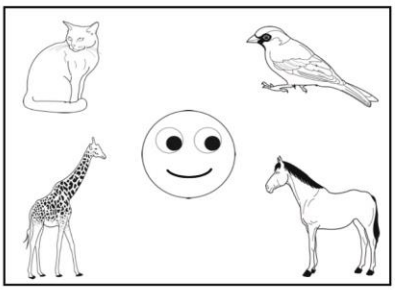
➲ Say: 'You are going to see some pictures, one in each corner of a box. You have to choose **which picture does the face like best.** Either point to or say which picture **the face likes best**. Please respond as quickly as possible.' Circle participant's choice. Correct items = 2 points, error = 1 point, egocentric error = 0 points.

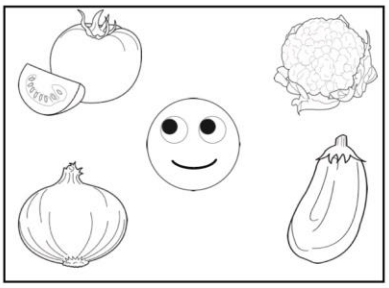
Score 0-12 ☐

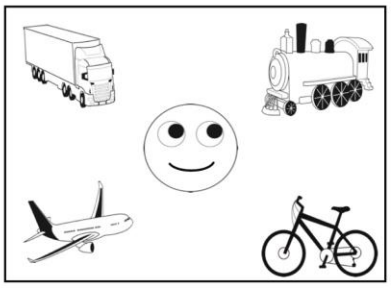












MEMORY – Delayed Recall

Scoring procedure for retention: obtain delayed recall performance (over page) and, together with immediate recall score, determine percentage retained. Convert percentage retained to Score using table below. If delayed recall = 0, score = 0.

Delayed recall to percentage retained calculation	Percentage retained to score conversion table

$$\frac{\text{(Delayed recall)}}{\text{(Immediate recall score)}} \quad x\ 100 = \%\ \textit{retained}$$

$$\frac{(\ldots\ldots\ldots\ldots\ldots\ldots)}{(\ldots\ldots\ldots\ldots\ldots\ldots)} \quad x\ 100 = \ldots\ldots\ldots\ldots\%\ \textit{retained}$$

Percentage retained	**Score**	Percentage retained	**Score**
1-10%	**1**	51-60%	**6**
11-20%	**2**	61-70%	**7**
21-30%	**3**	71-80%	**8**
31-40%	**4**	81-90%	**9**
41-50%	**5**	91-100+ %	**10**

➲ Say: 'At the beginning of this interview, I read you a short story. Tell me as much as you can remember from that story'. Mark 1 point for each (either entire or part of) underlined section recalled.

Three fishing boats helped rescue a whale that swam too close to the shore. The whale was spotted swimming in circles. Alan Williams from the Marine Conservation Trust said thirty-two young whales got lost last winter when looking for food.

Delayed recall =

Score (0-10) ☐

MEMORY – Delayed Recognition

If all items recalled, skip and score 4. Otherwise ask questions below.

Say: 'Let's see if you can remember anything more about that story. I will ask you some questions, please tell me if they are true or false'.

Circle responses (true or false) and mark 1 point for each item recognised in this section. Use table below to calculate score.

Score 0-4 ☐

Were there four fishing boats?	T	**F**	1
Was the story about rescuing dolphins?	T	**F**	1
Did this take place close to the shore?	**T**	F	1
Was the animal swimming in circles?	**T**	F	1
Was the man in the story called Mr. Williams?	**T**	F	1
Was his first name Stephen?	T	**F**	1
Were thirty-two whales lost last Summer?	T	**F**	1
Were the lost whales looking for food?	**T**	F	1

Recognition to recognition score table

Number of correct answers	**Score**
0-4	**0**
5	**1**
6	**2**
7	**3**
8	**4**

SCORES

Language	Naming, Comprehension, Spelling	/28
Verbal Fluency	Fluency Letter F, Fluency Letter D	/24
Executive	Reverse Digit Span, Alternation, Sentence Completion, Social Cognition	/48
	ALS-SPECIFIC:	**/100**
Memory	*Immediate recall, Delayed recall score, Delayed recognition*	*/24*
Visuospatial	*Dot Counting, Cube Counting, Number Location*	*/12*
	ALS NON-SPECIFIC:	***/36***
	ECAS TOTAL SCORE:	**/136**

EDINBURGH COGNITIVE and BEHAVIOURAL ALS SCREEN – ECAS
English Version (2013)

BEHAVIOUR SCREEN – Carer Interview

➲ Please ask the carer about the following possible behaviours. Symptoms should have occurred repeatedly and not just on one instance, and may have occurred prior to the development of any motor signs. Tick 'Yes', 'No' or 'Don't Know'. If 'Yes', please provide a brief written description. Give one mark for every 'Yes' response (maximum = 10).

A	**Behavioural disinhibition**				BEHAVIOUR
1	Socially inappropriate behaviour, e.g. *inappropriate behaviour with strangers* *criminal behaviour*	Y	N	DK	
2	Loss of manners or decorum, e.g. *crude or sexually explicit remarks, jokes or opinions that may be offensive to others* *lack of response to social cues*	Y	N	DK	
3	Impulsive, rash or careless actions, e.g. *new onset gambling, or buying or selling property without regard for consequences* *giving out personal information inappropriately, e.g. credit card numbers*	Y	N	DK	
B	**Apathy or inertia**				
4	Loss of interest, drive or motivation, e.g. *passivity and lack of spontaneity* *needs prompting to initiate or continue routine activities*	Y	N	DK	
C	**Loss of sympathy or empathy**				
5	Diminished response to other people's needs and feelings *Positive rating on this feature should be based on specific examples that reflect a lack of understanding or indifference to other people's feelings, e.g* *hurtful comments* *disregard for others' pain or distress*	Y	N	DK	
6	Diminished social interest, interrelatedness, personal warmth or general closeness in social engagement, e.g. *coldness* *lack of eye contact*	Y	N	DK	
D	**Perseverative, stereotyped, compulsive or ritualistic behaviour**				
7	Simple repetitive movements, e.g. *tapping, clapping* *scratching, picking skin or clothing* *repeating words*	Y	N	DK	
8	Complex, compulsive or ritualistic behaviours, e.g. *counting, cleaning rituals, checking* *collecting, hoarding*	Y	N	DK	

E	**Hyperorality and altered food preferences**				
9	Altered food preferences, e.g. *food fads* *carbohydrate craving (particularly sweets)*	Y	N	DK	
10	Binge eating or hyperorality, e.g., *cramming or continuing to eat despite satiety* *oral exploration or consumption of inedible objects*	Y	N	DK	
SCORE					
			TOTAL		***/10***

SYMPTOMS	
➲ Please tick box if at least one of the symptoms was present in each of the following categories.	
A. Behavioural disinhibition	
B. Apathy or inertia	
C. Loss of sympathy or empathy	
D. Perseverative, stereotyped, compulsive or ritualistic behaviour	
E. Hyperorality and altered food preferences	

ALS Psychosis Screen

➲ Please ask the carer about the following possible symptoms. Tick 'Yes', 'No' or 'Don't Know'. If 'Yes', please provide a brief written description. Give one mark for every 'Yes' response (maximum = 3).

1	Has strange and/or bizarre beliefs and behaviours	Y	N	DK
2	Hears or sees things that are not there, and/or feels the presence of someone who is not there	Y	N	DK
3	Is overly suspicious, and/or feels persecuted	Y	N	DK
SCORE				
		TOTAL		***/3***

ONSET AND DURATION OF SYMPTOMS		
➲ Please tick or complete box to indicate response.		
1. Do these symptoms represent a CHANGE from the patient's previous behaviour?	Y	N
If yes, did the changes occur:		
a. BEFORE the onset of the disease?	Y	N
b. at the same time as other symptoms?	Y	N
c. AFTER the onset of the disease?	Y	N
2. Do they still persist?	Y	N
3. If not, how long did they last?		

EDINBURGH COGNITIVE AND BEHAVIOURAL ALS SCREEN – ECAS
English Version C (2017)

Date of testing: .....
Age at leaving full-time education: .....
Occupation: .....
.....
Handedness: .....

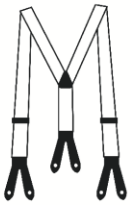
Name: .....
Date of Birth: .....
Hospital No. or Address: .....
.....
.....

LANGUAGE - Naming

➲ Ask: Say or write down the names of these pictures:

Score 0-8 ☐


.....☐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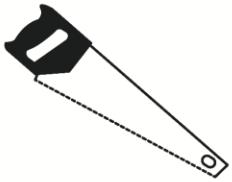
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LANGUAGE - Comprehension

➲ Ask: point to the one which is:

Score 0-8 ☐

1. An insect.....
2. Something a carpenter uses.....
3. Something with feathers.....
4. A place to sleep.....
5. Something you wear.....
6. Something you play.....
7. Something used to cut wood.....
8. An animal that lives in water.....

MEMORY – Immediate recall

Score 0-10 ☐

Also use this score to calculate % retention later

➲ Say: 'I am going to read you a short story. Please listen carefully. When I am finished, say or write as much as you can remember'. Score 1 point for each (either entire or part of) underlined section recalled.

Helen Blake, from Leeds has been awarded the Northern Art Prize for photography. The forty-seven year old started taking photos while hiking. Helen beat seven hundred competitors with her picture of an oak tree in autumn colours.

LANGUAGE - Spelling

Score 0-12 ☐

➲ Say: 'Spell, either by writing or speaking, the following words.' If the person is using assistive technology, ask them to turn off any predictive text facility.

1. Portrait	.....	2. Babysitter	.....
3. Entertaining	.....	4. Reduction	.....
5. Aquarium	.....	6. Lifeguard	.....
7. Borrow	.....	8. Suggested	.....
9. Headlight	.....	10. Schedule	.....
11. Wheelbarrow	.....	12. Wrote	.....

FLUENCY - Letter P

No. of correct words =

Time to copy/ read aloud =

➲ Say: 'I am going to give you a letter of the alphabet and I would like you to say or write as many different words as you can beginning with that letter, but not names of people or places, or numbers.'
- If writing, say: 'You will have **two** minutes. The letter is P.'
- If speaking, say 'You will have **one** minute. The letter is P.'

➲ Next the person copies/reads these words aloud.
- If writing, say: 'copy these words as fast as possible. I will time you. Ready? Begin.'

If speaking, say: 'read aloud these words as fast as possible. Before you do this, check that you can read them. I will time you. Ready? Begin.'

Verbal Fluency Index (Vfi) calculation:

If spoken:
Vfi = 60seconds – no. of seconds to read aloud words / No. of correct words generated

If written:
Vfi = 120seconds – no. of seconds to copy words / No. of correct words generated

VFI conversion to score table

SPOKEN VFI	WRITTEN VFI	Score
≥ 12.00	≥ 20.00	**0**
10.00 to < 12.00	16.50 to < 20.00	**2**
8.00 to < 10.00	13.00 to < 16.50	**4**
6.00 to < 8.00	9.50 to < 13.00	**6**
4.00 to < 6.00	6.00 to < 9.50	**8**
2.00 to < 4.00	2.50 to < 6.00	**10**
< 2.00	< 2.50	**12**

Score 0-12 ☐

EXECUTIVE – Reverse Digit Span

➲ Say: 'I am going to say some numbers and I would like you to say them back to me in reverse order. For example, if I say '2 3 4', you should say '4 3 2'. Let's have a practice. If I say '7 1 9', what would you say?' Stop when person gets both trials of a line wrong. Score total number of trials correct.

Score 0-12 ☐

Trial		Check	Trial		Check
1	3 1		**2**	8 4	
3	7 2 5		**4**	9 6 4	
5	1 8 4 6		**6**	7 3 6 8	
7	4 9 6 1 3		**8**	1 8 9 7 5	
9	5 6 1 4 9 2		**10**	2 7 3 4 8 1	
11	6 2 7 9 1 4 3		**12**	7 6 8 9 2 3 5	

EXECUTIVE – Alternation

➲ Say: 'I want you to alternate between numbers and letters, starting with 1-A, then 2-B, 3-C, and so on. Please alternate between numbers and letters, in order, without skipping any until I tell you to stop. Let's begin together: 1-A, 2-B, 3-C…'

Score 0-12 ☐

Trial		Check	Trial		Check	Trial		Check	Trial		Check
1	4-D		**2**	5-E		**3**	6-F		**4**	7-G	
5	8-H		**6**	9-I		**7**	10-J		**8**	11-K	
9	12-L		**10**	13-M		**11**	14-N		**12**	15-O	

FLUENCY - Letter M

➲ Say: 'I am going to give you a letter of the alphabet and I would like you to say or write as many different words as you can beginning with that letter, but not names of people or places, or numbers. This time the word must only be four letters long. No more or less than four letters'

- If writing, say: 'You will have **two** minutes. The letter is M.'
- If speaking, say 'You will have **one** minute. The letter is M.'

No. of correct words =

Time to copy/ read aloud =

➲ Next the person copies/reads these words aloud.

- If writing, say: 'copy these words as fast as possible. I will time you. Ready? Begin.'

If speaking, say: 'read aloud these words as fast as possible. Before you do this, check that you can read them. I will time you. Ready? Begin.'

Verbal Fluency Index (Vfi) calculation:

If spoken:

$$Vfi = \frac{60\text{seconds} - \text{no. of seconds to read aloud words}}{\text{No. of correct words generated}}$$

If written:

$$Vfi = \frac{120\text{seconds} - \text{no. of seconds to copy words}}{\text{No. of correct words generated}}$$

VFI conversion to score table

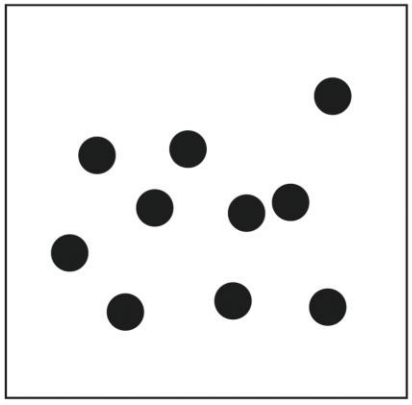
SPOKEN VFI	WRITTEN VFI	Score
≥ 20.00	≥ 27.25	**0**
16.75 to < 20.00	23.00 to < 27.25	**2**
13.50 to < 16.75	18.75 to < 23.00	**4**
10.25 to < 13.50	14.50 to < 18.75	**6**
7.00 to < 10.25	10.25 to < 14.50	**8**
3.75 to < 7.00	6.00 to < 10.25	**10**
< 3.75	< 6.00	**12**

Score 0-12 ☐

VISUOSPATIAL – Dot Counting

➲ Say: 'I would like you to count how many dots are in each box, but without pointing to them.'

Score 0-4 ☐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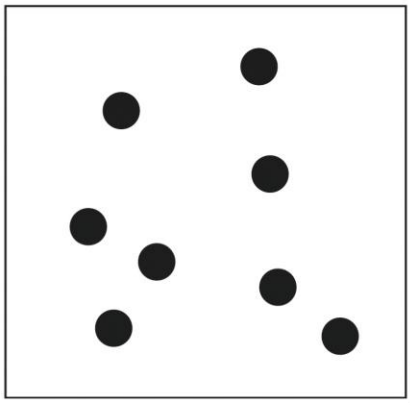
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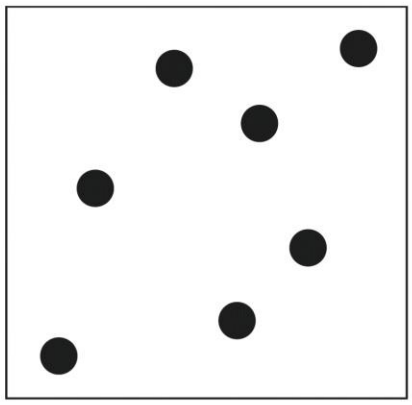
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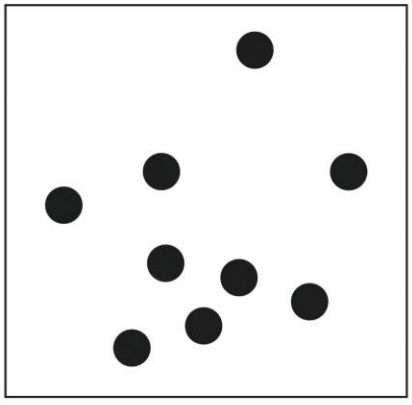
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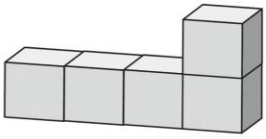
VISUOSPATIAL – Cube Counting

➲ Say: 'How many cubes are in each structure, including the ones you may not be able to see?'

Score 0-4 ☐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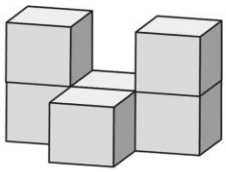
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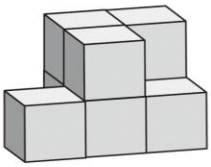
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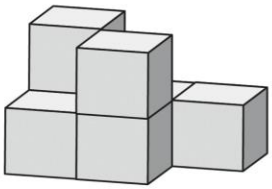
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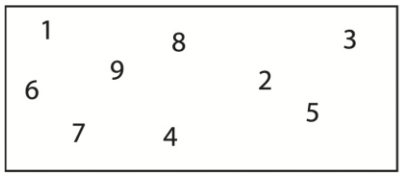
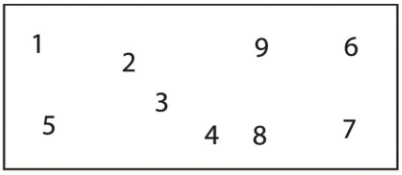
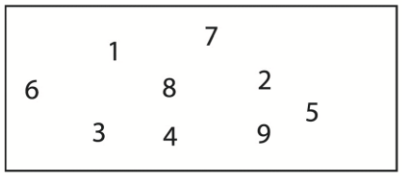
VISUOSPATIAL – Number Location

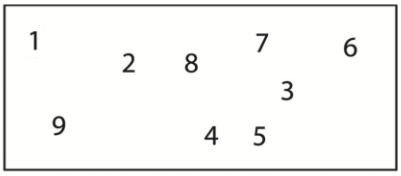
➲ Say: 'Which number corresponds to the position of the dot?'

Score 0-4









EXECUTIVE – Sentence Completion

➲ Say: 'Listen carefully to these sentences and as soon as I have finished reading them, please tell me, or write, a word that finishes the sentence as quickly as possible. For example, '*She was so tired that she went straight to…bed*'. Do not score.

1. He phoned up the restaurant to reserve a .....
2. When she got up in the morning, the sun was.....

➲ Say: 'Now I'd like you to do that again, but this time the word you give should not make sense whatsoever in the context of the sentence. It must not be related to the word that actually completes the sentence. For example, '*John cut his hand with the sharp…orange*'. If the person does not respond within 20 seconds, move onto the next question.

1. Lisa went to the library to return some .....

2. After her shower, she dried herself with a .....

3. He put a teabag in his mug and boiled the .....

4. He studied medicine to become a .....

5. The music started and everyone got up to .....

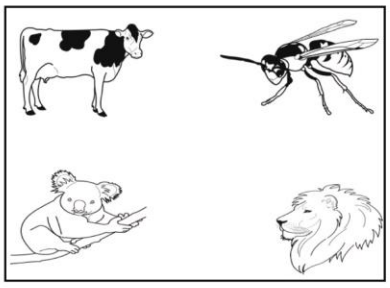
6. John picked up the leash and took his dog for a .....

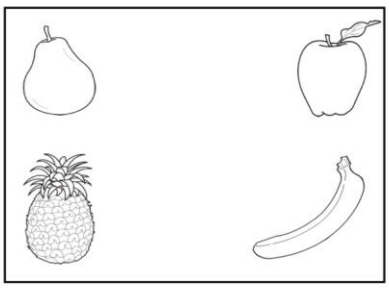
Give 2 points for different word, 1 point for related word (e.g. associated or opposite meaning) or 0 points for exact word.

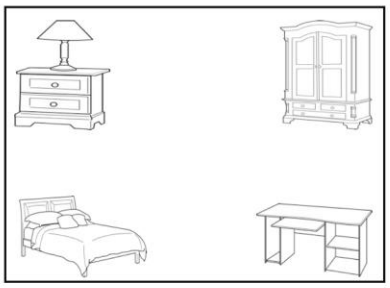
Score 0-12 ☐

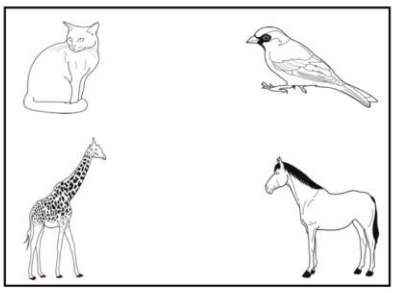
SOCIAL COGNITION – Part A

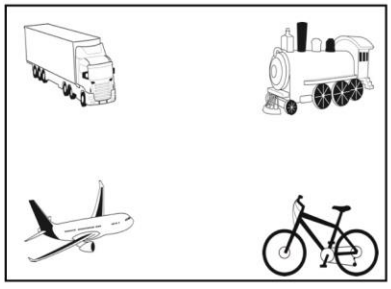
➲ Say: 'You are going to see some pictures, one in each corner of a box. You have to choose **which picture you like best.** Either point to or say which picture you like best. Please respond as quickly as possible.' Circle participant's choice.







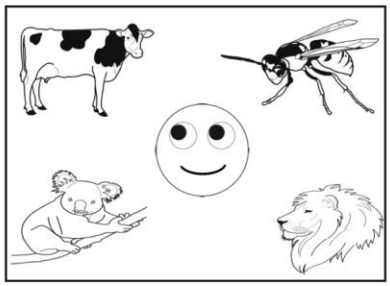


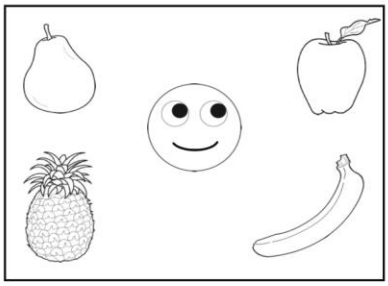


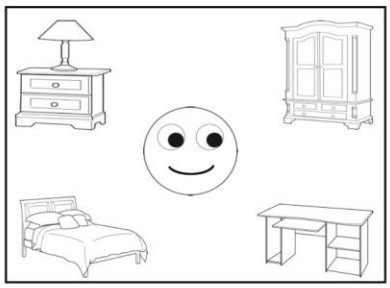
SOCIAL COGNITION – Part B

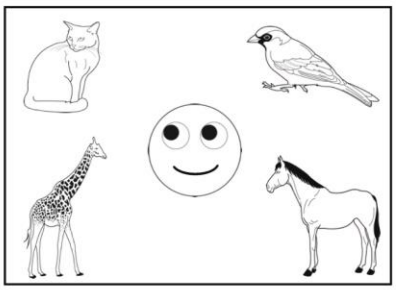
➲ Say: 'You are going to see some pictures, one in each corner of a box. You have to choose **which picture does the face like best.** Either point to or say which picture **the face likes best**. Please respond as quickly as possible.' Circle participant's choice. Correct items = 2 points, error = 1 point, egocentric error = 0 points.

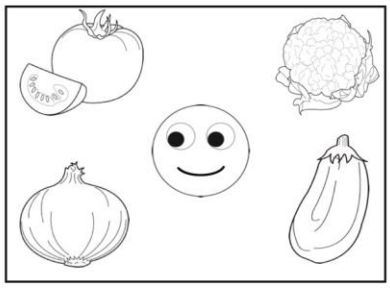
Score 0-12 ☐

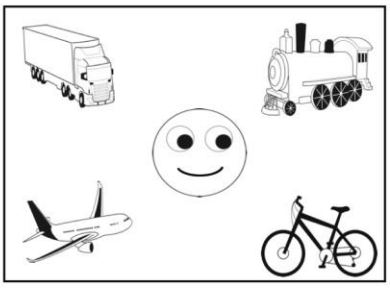












MEMORY – Delayed Recall

Scoring procedure for retention: obtain delayed recall performance (over page) and, together with immediate recall score, determine percentage retained. Convert percentage retained to Score using table below. If delayed recall = 0, score = 0.

Delayed recall to percentage retained calculation	Percentage retained to score conversion table

$$\frac{\text{(Delayed recall)}}{\text{(Immediate recall score)}} \quad x\ 100 = \%\ \textit{retained}$$

$$\frac{(\ldots\ldots\ldots\ldots\ldots\ldots)}{(\ldots\ldots\ldots\ldots\ldots\ldots)} \quad x\ 100 = \ldots\ldots\ldots\ldots\%\ \textit{retained}$$

Percentage retained	**Score**	Percentage retained	**Score**
1-10%	**1**	51-60%	**6**
11-20%	**2**	61-70%	**7**
21-30%	**3**	71-80%	**8**
31-40%	**4**	81-90%	**9**
41-50%	**5**	91-100+ %	**10**

➲ Say: 'At the beginning of this interview, I read you a short story. Tell me as much as you can remember from that story'. Mark 1 point for each (either entire or part of) underlined section recalled.

Helen Blake, from Leeds has been awarded the Northern Art Prize for photography. The forty-seven year old started taking photos while hiking. Helen beat seven hundred competitors with her picture of an oak tree in autumn colours.

Delayed recall
=

Score (0-10) ☐

MEMORY – Delayed Recognition

If all items recalled, skip and score 4. Otherwise ask questions below.

Say: 'Let's see if you can remember anything more about that story. I will ask you some questions, please tell me if they are true or false'.

Circle responses (true or false) and mark 1 point for each item recognised in this section. Use table below to calculate score.

Score 0-4 ☐

Was the woman in the story called Helen?	**T**	F	1
Was her second name Smith?	T	**F**	1
Was she from Leeds?	**T**	F	1
Did the woman in the story win the Northern Art Prize?	**T**	F	1
Was her prize for painting?	T	**F**	1
Were there nine hundred competitors?	T	**F**	1
Was the woman's picture of an oak tree?	**T**	F	1
Was the woman's picture in winter colours?	T	**F**	1

Recognition to recognition score table	
Number of correct answers	**Score**
0-4	**0**
5	**1**
6	**2**
7	**3**
8	**4**

SCORES

Language	Naming, Comprehension, Spelling	/28
Verbal Fluency	Fluency Letter P, Fluency Letter M	/24
Executive	Reverse Digit Span, Alternation, Sentence Completion, Social Cognition	/48
	ALS-SPECIFIC:	**/100**
Memory	*Immediate recall, Delayed recall score, Delayed recognition*	*/24*
Visuospatial	*Dot Counting, Cube Counting, Number Location*	*/12*
	ALS NON-SPECIFIC:	***/36***
	ECAS TOTAL SCORE:	**/136**

EDINBURGH COGNITIVE and BEHAVIOURAL ALS SCREEN – ECAS
English Version (2013)

BEHAVIOUR SCREEN – Carer Interview

➲ Please ask the carer about the following possible behaviours. Symptoms should have occurred repeatedly and not just on one instance, and may have occurred prior to the development of any motor signs. Tick 'Yes', 'No' or 'Don't Know'. If 'Yes', please provide a brief written description. Give one mark for every 'Yes' response (maximum = 10).

A	**Behavioural disinhibition**			
1	Socially inappropriate behaviour, e.g. *inappropriate behaviour with strangers* *criminal behaviour*	Y	N	DK
2	Loss of manners or decorum, e.g. *crude or sexually explicit remarks, jokes or opinions that may be offensive to others* *lack of response to social cues*	Y	N	DK
3	Impulsive, rash or careless actions, e.g. *new onset gambling, or buying or selling property without regard for consequences* *giving out personal information inappropriately, e.g. credit card numbers*	Y	N	DK
B	**Apathy or inertia**			
4	Loss of interest, drive or motivation, e.g. *passivity and lack of spontaneity* *needs prompting to initiate or continue routine activities*	Y	N	DK
C	**Loss of sympathy or empathy**			
5	Diminished response to other people's needs and feelings *Positive rating on this feature should be based on specific examples that reflect a lack of understanding or indifference to other people's feelings, e.g* *hurtful comments* *disregard for others' pain or distress*	Y	N	DK
6	Diminished social interest, interrelatedness, personal warmth or general closeness in social engagement, e.g. *coldness* *lack of eye contact*	Y	N	DK
D	**Perseverative, stereotyped, compulsive or ritualistic behaviour**			
7	Simple repetitive movements, e.g. *tapping, clapping* *scratching, picking skin or clothing* *repeating words*	Y	N	DK
8	Complex, compulsive or ritualistic behaviours, e.g. *counting, cleaning rituals, checking* *collecting, hoarding*	Y	N	DK

BEHAVIOUR

E	**Hyperorality and altered food preferences**				
9	Altered food preferences, e.g. *food fads* *carbohydrate craving (particularly sweets)*	Y	N	DK	
10	Binge eating or hyperorality, e.g., *cramming or continuing to eat despite satiety* *oral exploration or consumption of inedible objects*	Y	N	DK	
SCORE					
	TOTAL				***/10***

SYMPTOMS	
➲ Please tick box if at least one of the symptoms was present in each of the following categories.	
A. Behavioural disinhibition	
B. Apathy or inertia	
C. Loss of sympathy or empathy	
D. Perseverative, stereotyped, compulsive or ritualistic behaviour	
E. Hyperorality and altered food preferences	

ALS Psychosis Screen

➲ Please ask the carer about the following possible symptoms. Tick 'Yes', 'No' or 'Don't Know'. If 'Yes', please provide a brief written description. Give one mark for every 'Yes' response (maximum = 3).

1	Has strange and/or bizarre beliefs and behaviours	Y	N	DK
2	Hears or sees things that are not there, and/or feels the presence of someone who is not there	Y	N	DK
3	Is overly suspicious, and/or feels persecuted	Y	N	DK
SCORE				
	TOTAL			***/3***

ONSET AND DURATION OF SYMPTOMS		
➲ Please tick or complete box to indicate response.		
1. Do these symptoms represent a CHANGE from the patient's previous behaviour?	Y	N
If yes, did the changes occur:		
a. BEFORE the onset of the disease?	Y	N
b. at the same time as other symptoms?	Y	N
c. AFTER the onset of the disease?	Y	N
2. Do they still persist?	Y	N
3. If not, how long did they last?		

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS)
Administration and Guidance Notes 2013
English Version A

The ECAS is a practical screening tool that incorporates a range of short cognitive tests that have been shown to be sensitive to cognitive impairment in ALS. The ECAS has been designed to differentiate between the different profiles common with ageing including depression, Alzheimer's disease and Frontotemporal Dementia. Executive Functions, Memory, Language, Visuospatial skills and Social cognition are specifically assessed whilst a Behavioural and Psychosis brief interview can be carried out with carers or relatives. The ECAS is designed for ALS patients and answers can be given verbally, or by a combination of writing or pointing. It is suitable for patients who are anarthric or patients who have no hand motor function. The total score is 136 points and should take no longer than 15 minutes to administer. Two alternate versions of the ECAS (B and C) have been developed for situations where serial testing is required. **Specific guidance on the administration of ECAS B and C can be obtained at http://ecas.psy.ed.ac.uk/ or contacting s.abrahams@ed.ac.uk.**

Equipment required

To carry out the ECAS, you will need a clock or a watch with a second hand (though a stopwatch would be preferable). A calculator is recommended for calculations (though these can also be carried out by hand). Answers can be written or spoken, though should be spoken where possible. If answers are to be written, extra sheets of paper and a selection of pens that will suit the person's writing ability will be required.

Language – Naming: Score 0-8

Administration: There are eight pictures displayed. Ask the person to name the objects shown. No time limit is enforced for the task. Incorrect answers are recorded and no prompt for alternative word is provided. A correct score will only be given if the exact name is said or spelled correctly. Self-corrections are allowed; only the final answer is taken for scoring.

Scoring: One point is given for every correct name given. **Correct answers are (left to right, top to bottom); scorpion, bow, helicopter, fox, axe, squirrel, swan, accordion.**

Language – Comprehension: Score 0-8

Administration: Using the pictures from the naming task, ask the person to correctly answer the questions. Questions are either read by the person or to the person, depending on preference. Some questions will require the repetition of an earlier item to serve as an answer; participants are not warned about this in advance but this can be clarified if queried. If no answer is provided, answer space is to be left blank. Self-corrections are allowed; only the final answer is taken for scoring.

Scoring: One point is given for every correct answer given. **Correct answers are; helicopter, swan, squirrel, axe, helicopter, axe, scorpion, squirrel.**

Note: If the participant incorrectly names an item in the previous section, but identifies the correct item with the wrong name in the comprehension section, score as correct. For example, in the ECAS-A if the participant names the Scorpion as 'Lobster' in the naming section, but answers 'Lobster' when asked "Something with a sting" in the comprehension section, score as correct. In this instance, the person does not know the name of the item but does comprehend what it is.

Memory – Immediate recall: Score 0-10

Administration: Say: "*I am going to read you a short story. Please listen carefully. When I am finished, say or write as much as you can remember."*

Story should be read at a steady pace of 2 words per second/the story should take around 20 seconds to read out. When finished reading story aloud, say to participant ***"Now that's the end of the story, what can you remember?"*** Time for recall is unlimited, until participants say that they can remember no more. Self-corrections are allowed; only the final answer is taken for scoring.

Scoring: Score 1 point for each (either entire or part of) underlined section recalled. For example "annual litter collection" recalled as '*annual collection*' '*litter collection*' or '*annual rubbish collection*' would each score 1 point. Similarly, *'impressed and especially proud'* may be recalled as another positive emotional response to the event such as '*pleased*'. Number information must be recalled accurately, for example "Forty two people" recalled as '*forty something*' would score 0 points. This immediate recall score will **also** be used later on to calculate the percentage of memory retained over time. **No prompts should be given for specific information, only "is that everything you can remember" should be asked to confirm participant has finished recall.**

Language – Spelling: Score 0-12

Administration: Say *"Spell, either by writing or speaking, the following words."*

If the person is using assistive technology, ask them to turn off any predictive text facility. Unlimited time is given for spelling of each word. All words are assessed even if early words in the list are incorrect. Move on to the next word if participant is unable or unwilling to attempt spelling of one word. The word may be clearly stated by the interviewer several times if necessary. For example, if the participant spells 'constructing' as 'construction', restate the word clearly. Similarly, if the plural of the word is spelled e.g., 'biscuits' instead of 'biscuit', restate the target word clearly.

Scoring: Score 1 point for each correct spelling. Self-corrections are allowed; only the final answer is taken for scoring.

Caution should be taken in interpretation where low premorbid IQ or a history of reading or spelling difficulties is reported. It is recommended interviewer ask patient and/or carer about premorbid reading and writing abilities.

Fluency - Letter S: Score 0-12

Administration: The person can perform this task either by speaking or writing. Say: *"I am going to give you a letter of the alphabet and I would like you to say or write as many different words as you can beginning with that letter.* ***But not names of people or places, or numbers****.* If writing, say: "You will have two minutes and the letter is S." If speaking, say: "You will have one minute and the letter is S."

Next the person copies/repeats these words. If writing, say: "*Copy these words as fast as possible. I will time you. Ready? Begin."* If speaking, ensure the participant can read the words you have written, then say: "*Read aloud these words as fast as possible. Before you do this, check that you can read them. I will time you. Ready? Begin."*

Scoring: All answers provided are recorded however the following rules apply for scoring items as correct. Words must be varied for example: *sugar, salt, slipper, snow, scream, shoot, scale, scissors….*

Do not include repetitions, nonsense words (i.e. cannot be found in an English dictionary), or proper names in scoring items correct. Repetitions where a second meaning is provided (e.g. *'school - the educational institution'* or *'school - collective name of fish'*) are scored as independent items. Likewise, when items are spoken and a different spelling/meaning is indicated (e.g. *slow* and *sloe*) items are scored as independently correct. Where a meaning change is indicated (e.g. *savour* and *savoury*) items are scored as independently correct. Plural words will be accepted, only if they have not already been provided in singular form (e.g. *slipper, slippers* = score 1). Perseverations of words such as *sit, sat, sitting…* where meaning is not changed, are **not accepted as correct** (e.g. *sit, sat, sitting* = score 1, *take, took* = score 1).

In order to account for differences in motor speed and speaking time variations, a Verbal Fluency Index (VFI) is calculated using the equation below.

$$VFI = \frac{Test\ time - time\ taken\ to\ repeat\ words}{Number\ of\ correct\ words\ generated}$$

For example, a participant given 60 seconds to complete the task who generates 5 words and then takes 15 seconds to read these words aloud would have a VFI of 9:

$$\frac{60 - 15}{5} = VFI\ of\ 9$$

A participant's VFI is converted to a Fluency score using the conversion table provided in ECAS.

Executive – Backward Digit Span: Score 0-12

Administration: Numbers should be read out at a pace of 1 number per second. Say: *"I am going to say some numbers and I would like you to say them back to me in reverse order. For example, if I say '2 3 4', you should say '4 3 2'. Let's have a practice. If I say '7 1 9', what would you say?"*

If the participant makes an error on the practice trial, they are corrected and the first trial of the test begins. If the participant fails the first two items then the test is scored at 0 and no further items are attempted. Advance warning that the number sequences will increase in length is provided at the start of each line of a trial. In order to score a trial of a line as correct, participant must accurately recall all items in reverse order. No score is given for individual numbers correctly recalled in an incorrectly recalled sequence. If the participant gets at least one trial of a line correct, move on to the next line. Self-corrections are allowed; only the final answer is taken for scoring. Stop when person gets both trials of a line wrong.

Scoring: Score is total number of trials achieved correctly (out of 12).

Executive – Alternation: Score 0-12

Administration: Say*: "I want you to alternate between numbers and letters, starting with 1-A, then 2-B, 3-C, and so on. Please continue from there, alternating between numbers and letters, in order, without skipping any until I tell you to stop"*. Say: "*1-A, 2-B, 3-C..."* with the patient and then let them continue the sequence alone. If the patient alternates with the letter first and number second (e.g., A-1, B-2, C-3) score as correct if the sequence is retained.

Scoring: One point is given for every correct trial.

Fluency - Letter T: Score 0-12

Administration: The person can perform this task either by speaking or writing. Say: "*I am going to give you a letter of the alphabet and I would like you to say or write as many words as you can beginning with that letter.* ***But not names of people or places, or numbers****.* ***This time the word must only be four letters long. No more or less than four letters."*** Note: Plurals are accepted in order to create four letters – for example, *Toes.*

- If writing, say: "You will have two minutes and the letter is T."
- If speaking, say "You will have one minute and the letter is T."

Next the person copies/repeats these words.

- If writing, say: "*Copy these words as fast as possible. I will time you. Ready? Begin."*
- If speaking, say: "*Read aloud these words as fast as possible. Before you do this, check that you can read them. I will time you. Ready? Begin."*

Scoring: See scoring criteria from previous Fluency task to produce VFI, and conversion table provided in ECAS.

Visuospatial – Dot counting: Score 0-4

Administration: Say *"I would like you to count how many dots are in each box, but without pointing to them"*. Progress from left to right and top to bottom to move through the squares. All squares should be attempted.

Scoring: One point for each correct box. **Correct answers are: Top left 10, top right 8, bottom left 7, bottom right 9.**

Visuospatial – Cube counting: Score 0-4

Administration: Ask the person *"How many cubes are in each structure, including the ones you may not be able to see?"* Progress from left to right and top to bottom to move through the cube structures. All structures should be attempted.

Scoring: one point for each correct answer. **Correct answers are top left 5, top right 6, bottom left 10 and bottom right 7.**

Visuospatial – Number location: Score 0-4

Administration: Ask the person *"Which number corresponds to the position of the dot?'* Progress from left to right and top to bottom to move through the squares. All squares should be attempted.

Scoring: One point for each correct answer. **Correct answers are top left 6, top right 5, bottom left 2, bottom right 3**

Executive – Sentence completion: Score 0-12

Administration: Say *"Listen carefully to these sentences and as soon as I have finished reading them, please tell me, or write, a word that finishes the sentence as quickly as possible."* **For example, *'She was so tired that she went straight to…bed'*.** Do not score the first two questions.

Now say: *" I'd like you to do that again, but this time the word you give should not make sense whatsoever in the context of the sentence. It must not be related to the word that actually completes the sentence.* **For example, *'John cut his hand with the sharp…orange'*.** If person answers with a word which completes the sentence in context then remind them that the requirement is to provide an answer that bears no significance to the context of the sentence. Progress through all questions, even when incorrect answers are provided. If the person does not respond within 20 seconds, move onto the next question. Take the first answer generated by the participant, do not allow self-correction.

Scoring: Give 2 points for completely unconnected word, 1 for related word (e.g. **associated** or opposite meaning) and 0 for exact word. See table below for scoring examples. Note: sentences can be ungrammatical.

	Question	**2 points**	**1 point**	**0 points**
1	The postman knocked on the...	Car, potato...	Window, gate, mailbag...	Door
2	He brought his umbrella with him in case of...	Rubber, parachute...	Sunshine, wind, ice...	Rain
3	Sally spread her toast with butter and...	Earth, sand...	Cereal, egg, oranges...	Jam, Marmalade, Honey, Cheese
4	John went to the barber and got his hair...	Moon, table...	Washed, lengthened, singed...	Cut
5	She dived into the swimming...	Garden, swing...	Pond, bath, rock...	Pool
6	They all went to the local café for something to...	Jump, dance...	Do, play, buy...	Eat, drink.

Social Cognition – Part A

Administration: The first page contains six boxes each with four pictures in each corner.

Say: *"You are going to see some pictures, one in each corner of a box. You have to choose* ***which picture you like best.*** *Either point to or say which picture you like best. Please respond as quickly as possible."*

Scoring: Answers are recorded but not scored; responses are used as information to support scoring in the next section.

Social Cognition – Part B: Score 0-12

Administration: Say: "*You are going to see some pictures, one in each corner of a box. You have to choose which picture* ***does the face like best****. Either point to or say which* ***the face likes best****. Please respond as quickly as possible.'* Progress through all questions even when incorrect answers are provided. Test instructions can be repeated exactly as written, but **DO NOT amend or add to the instructions for this test, for example, do not say 'which is the face looking at'.** When guiding participants through the boxes, avoid pointing to any particular corner/picture.

Scoring: Two points for each correct response. Of the items not correctly identified, score 1 point if answer was NOT the item that participant picked as their own favourite in the previous section, score 0 points if the item WAS picked as their own favourite.

Memory – Delayed recall: Score 0-10

Administration: Say: *"At the beginning of this interview, I read you a story. Tell me as much as you can remember from that story."* Time for recall is unlimited, until participants say that they can remember no more. Self-corrections are allowed; only the final answer is taken for marking.

Scoring: 1 point for each (either entire or part of) underlined section recalled. The percentage of memory retained is now calculated. Take the total recall for **Delayed Memory and divide it by the Immediate Memory score, before multiplying this number by 100.** For example:

With a Delayed Memory recall of 8 sections, and an Immediate Memory Score of 9/10

The percentage of retained memory is 89%.

Some patients may recall more at delay than immediate and the percentage will be displayed as being over 100%. **Use the conversion table provided in ECAS to derive scoring.**

Memory – Delayed recognition: Score 0-4

Administration: This test should only be done if the person failed to recall one or more items. If all the items were recalled, skip the test and score 4.

Otherwise, say: *"Let's see if you can remember anything more about that story. I will ask you some questions, please tell me if they are **true or false**"*. If they patient responds "don't know" to any question, ask the patient to provide a best guess.

Scoring: Score 1 point for each correct answer; correct answers are marked in bold in this section. If the person gives a "**don't know**" answer ask them to make a guess on True or False and score accordingly. **Use the conversion table provided in ECAS to derive final scoring for recognition section.**

Total and Domain Scores & Abnormality Cut Offs

DOMAIN	SUBTESTS	MAX SCORE	CUT OFF FOR ABNORMALITY
Language	Naming, Comprehension, Spelling	/28	26
Verbal Fluency	Fluency Letter S, Fluency Letter T	/24	14
Executive	Reverse Digit Span, Alternation, Sentence Completion, Social Cognition	/48	33
	ALS-SPECIFIC:	**/100**	**77**
Memory	*Immediate recall, Delayed recall score, Delayed recognition*	*/24*	*13*
Visuospatial	*Dot Counting, Cube Counting, Number Location*	*/12*	*10*
	ALS NON-SPECIFIC:	**/36**	**24**
	ECAS TOTAL SCORE	**/136**	**105**

ALS Carer Behaviour Screen
Guidance and Administration
English Version

Guidance: Please complete this interview with the carer or relative in private from the patient, ideally in a separate room. There are five components to this screen. Some people may have noticed a change in all areas, some in a few, and others may note there are no changes with the patient. Please prompt the carer or relative to give any examples if possible, which should be recorded on the form. The ECAS Behaviour Screen is interview based and should therefore be complete with the carer or relative.

UNDER NO CIRCUMSTANCES SHOULD IT BE GIVEN TO THE CARER OR RELATIVE TO COMPLETE ON THEIR OWN.

Administration: Please ask the carer about the listed possible behaviours. Symptoms should have occurred **repeatedly** and not just on one instance, and may have occurred prior to the development of any motor signs. Tick 'Yes', 'No', or 'Don't Know'. If 'Yes', please provide a brief written description.

Scoring: Give one mark for every 'Yes' response (range = 0-10)

ALS – Psychosis Screen
Guidance and Administration
English Version

Guidance: Please complete this interview with the carer or relative in private from the patient, ideally in a separate room. Please remind the carer or relative that the questions asked are only relevant since the onset of ALS.

Administration: Please ask the carer about the following possible symptoms. Tick 'Yes', 'No' or 'Don't Know'. If 'Yes', please provide a brief written description.

Scoring: Give one mark for every 'Yes' response (range = 0-3).

Guidelines for Translation

We provide below guidelines for translation however after reading and considering these points, you may wish to contact Dr Thomas Bak and Professor Sharon Abrahams to coordinate all language and culturally specific issues, thomas.bak@ed.ac.uk, s.abrahams@ed.ac.uk.

Good practice would require a naïve researcher who is fluent in both the language of translation and in English to back-translate the new version into English, in order to see that any translation accurately matches the original English version.

Language - Naming

If items are not easy to translate into local language and culture choice of items for selection can be made via the following criteria: half the items should be living, and half non-living. Within the non-living category, manipulable and non-manipulable objects should be included. One option would be to include one tool, one musical instrument, one item of clothing and one vehicle (as is the case in ECAS English version). Frequency of items selected should be low enough that items are not easy to name, yet not so high that they cannot be named by all controls.

Note: monochrome drawings are recommended to facilitate photocopying.

Language - Comprehension

Items should include questions where understanding depends on a verb (for example, "*something used for chopping*", "*something that you can fly in*"). Ideally comprehension should include different grammatical constructions (for example, "*something with a sharp edge*").

Note: it is better to avoid having one question pertaining to each naming item because patients can then predict later answers by a process of elimination rather than comprehension.

Memory – Immediate recall

Story should be adapted to local culture where necessary.

Language - Spelling

Items should include, in comparable numbers, nouns, verbs and compound words. Compound words should consist of noun-verb combinations.

Items should be of a low-to-medium frequency such that most controls should be able to spell items yet not so high that all controls can spell all items.

specified amount of letters should have a similar frequency in language of conversion to that of words beginning with letter T and consisting of four letters in English.

In our experience written and spoken verbal fluency performance is comparable after VFI calculation. Data is, however, still being collected and this opinion may be revised in light of data collected in 2013.

Each translated ECAS should collect relevant control data and corresponding conversion tables should be constructed. The technique for producing conversion tables is provided below and should be derived from the data of at least 40 healthy controls, with 20 of these healthy controls providing spoken responses and the other 20 healthy controls providing written responses.

Performance bracket	**Converted score**
≥ X + 6.75 SD	**0**
X + 5.25 SD to X + 6.74 SD	**2**
X + 3.75 SD to X + 5.24 SD	**4**
X + 2.25 SD to X + 3.74 SD	**6**
X + 0.75 SD to X + 2.24 SD	**8**
X – 0.75 SD to X + 0.74 SD	**10**
< X – 0.76 SD	**12**

Where X = healthy control mean, and SD = healthy control standard deviation

Executive – Sentence completion

Translation of this task requires a language specialist and researchers should contact Dr Thomas Bak, as above.

In alphabetic languages words should be mid-length, polysyllabic words.

In morphologically complex languages we would encourage use of different grammatical forms of words (past tense, continuous, inflected nouns etc.)

Verbal Fluency - Letter

Letters to use are at the discretion of the researcher however, the prevalence of words beginning with the letter should have a similar frequency in language of conversion to that of words beginning with letter S in English.

In our experience written and spoken verbal fluency performance is comparable after VFI calculation. Data is, however, still being collected and this opinion may be revised in light of data collected in 2013.

Each translated ECAS should collect relevant control data and corresponding conversion tables should be constructed. The technique for producing conversion tables is provided below and should be derived from the data of at least 40 healthy controls, with 20 of these healthy controls providing spoken responses and the other 20 healthy controls providing written responses.

Performance bracket	**Converted score**
≥ X + 6.75 SD	**0**
X + 5.25 SD to X + 6.74 SD	**2**
X + 3.75 SD to X + 5.24 SD	**4**
X + 2.25 SD to X + 3.74 SD	**6**
X + 0.75 SD to X + 2.24 SD	**8**
X – 0.75 SD to X + 0.74 SD	**10**
< X – 0.76 SD	**12**

Where X = healthy control mean, and SD = healthy control standard deviation

Verbal Fluency – Letter and restricted number of letter

IT IS VERY IMPORTANT IN THIS LETTER FLUENCY CONDITION TO SPECIFY THE NUMBER OF LETTERS (e.g. in English, words consisting of 4 letters, beginning with the letter T). THIS IS BECAUSE RESTRICTED VERBAL FLUENCY IS MORE DEMANDING THAN UNRESTRICTED VERBAL FLUENCY

Letters to use are at the discretion of the local researcher who will have knowledge on typical letters used in fluency in their local language. However, **the prevalence of words beginning with the given letter and consisting of the**

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS)
Administration and Guidance Notes 2017
English Version B & C

The ECAS is a practical screening tool that incorporates a range of short cognitive tests that have been shown to be sensitive to cognitive impairment in ALS. Two alternate versions of the ECAS (B and C) have been developed for situations where repeated assessment is required. Specific guidance on the administration of ECAS A can be obtained at http://ecas.psy.ed.ac.uk/ or by contacting s.abrahams@ed.ac.uk. **These guidelines provide additional information on Versions, B, and C. Unless otherwise stated, administration and scoring of Versions B and C are unchanged from Version A and the original guidelines should be used.**

Language – Naming: Score 0-8

Version B Scoring: One point is given for every correct name given. **Correct answers (left to right, top to bottom): Peacock, waistcoat, tractor, zebra, spanner/wrench, hedgehog, owl, tambourine.**

Version C Scoring: One point is given for every correct name given. **Correct answers (left to right, top to bottom): Ladybird, braces, caravan, deer, saw, octopus/squid, parrot, and saxophone.** Some items in ECAS-C have accepted alternatives. See table below.

ECAS-C	Accepted alternatives ECAS-C	Alternatives Not Accepted ECAS-C
Ladybird	Ladybug	Insect, beetle
Braces	Suspenders	Rope, letter M
Caravan	-	Trailer
Deer	Stag, Reindeer	Moose
Saxophone	-	Trumpet

Language – Comprehension: Score 0-8

Version B Scoring: One point is given for every correct name given. **Correct answers (left to right, top to bottom): Waistcoat, peacock, tambourine, tractor, spanner/wrench, hedgehog, tractor, zebra.**

Version C Scoring: One point is given for every correct name given. **Correct answers (left to right, top to bottom): ladybird, saw, parrot, caravan, braces, saxophone, saw, octopus.**

Note: If the participant incorrectly *names* an item in the previous section, but *identifies* the correct item with the wrong name in the comprehension section, score as correct. For example, in the ECAS-A if the participant names the Scorpion as 'Lobster' in the naming section, but answers 'Lobster' when asked *"Something with a sting"* in the comprehension section, score as correct. In this instance, the person does not know the name of the item but does comprehend what it is.

Memory – Immediate recall: Score 0-10

Version B Scoring: Score 1 point for each (either entire or part of) underlined section recalled.

Item	Accepted responses
Three	Only the correct number 'three' is accepted
Fishing boats	'Fishing' and/or 'boats'. If the participant correctly identifies one meaning of this item, score as correct e.g., 'fishermen' is accepted, as is 'sailing boats'.
Rescue	'Helped', 'rescue', or 'saved' are accepted
Whale	Only 'whale' or 'whales' are accepted
Shore	'Shore' or responses with similar meaning are accepted e.g., 'near the beach', or 'just off the coast' are accepted
Circles	Close synonyms or responses with similar meaning should be scored as correct e.g., 'the whales were going round and round'.
Alan Williams	Score correct if the participant identifies either 'Alan', or 'Williams' or both.
Marine conservation trust	Score correct if any part of 'marine conservation trust' is recalled verbatim. Accepted responses may be semantically similar, for example, 'animal', 'nature', or 'wildlife' for *marine*. Similarly, 'board', 'group' or 'council' may be accepted for *trust*.
Thirty-two	Only the exact number 'thirty-two' is accepted.
Last winter	'Last winter' or 'this winter' are accepted. 'Last Summer' or 'this year' should not be accepted.

Version C Scoring: Score 1 point for each (either entire or part of) underlined section recalled.

Item	Acceptable responses
Helen Blake	Either 'Helen' and/or 'Blake' is accepted.
Leeds	'Leeds' only.
Northern	'Northern' or 'north' only.
Prize	'Prize', 'award', or 'competition' accepted.
Photography	'Photography', 'photographs', 'photographer'.
Forty-seven	'Forty-seven' only.
Hiking	'Walking in the country' is accepted, whereas just 'walking' is not.
Seven hundred	'Seven hundred' only.
Oak tree	'Oak', or 'oak tree' is accepted.
Autumn	'Autumns colours', 'Autumn leaves', 'autumnal' or just 'autumn' are accepted. 'Golden leaves' is not accepted.

Language – Spelling: Score 0-12

Administration: Say "*Spell, either by writing or speaking, the following words.*"

For Version B, it may be necessary to clarify item 12, 'thought'. If so, say: "I thought dinner was at eight o'clock". For Version C, It may be necessary to clarify item 12, 'wrote'. If so, say: "I wrote a letter".

Fluency - Letters S/F/P: Score 0-12

Instructions as in Version A.

Executive – Backward Digit Span: Score 0-12

Instructions as in Version A.

Executive – Alternation: Score 0-12

Instructions as in Version A.

Fluency - Letter T/D/M: Score 0-12

For Version C, ensure that the letter 'M' is said clearly to avoid the participant mishearing. It may be necessary on occasion to specify, for example, say: *"'M' as in mother".*

Visuospatial – Dot counting: Score 0-4

Instructions as in Version A.

Visuospatial – Cube counting: Score 0-4

Version B Scoring: One point for each correct answer. **Correct answers are top left 5, top right 6, bottom left 10, and bottom right 7.**

Version C Scoring: One point for each correct answer. **Correct answers are top left 5, top right 6, bottom left 8, and bottom right 7.**

Visuospatial – Number location: Score 0-4

Version B Scoring: one point for each correct answer. **Correct answers are top left 7, top right 8, bottom left 4, and bottom right 3.**

Version C Scoring: one point for each correct answer. **Correct answers are top left 1, top right 8, bottom left 5, and bottom right 7.**

Executive – Sentence completion: Score 0-12

Scoring (all versions): Give 2 points for completely unconnected word, 1 for related word (e.g., associated or opposite meaning) and 0 for exact word. See table below for scoring examples. Note: sentences can be ungrammatical.

VERSION B				
	Item	**2 points**	**1 point**	**0 points**
1	She answered the phone because it was…	Purple, dangerous, sunny…	Silent, talking…	Ringing, buzzing
2	The joke was so funny, he started to…	Undress, walk, disappear…	Cry, snore, fall asleep…	Laugh, giggle, chuckle
3	Daniel unlocked the door with a…	Balloon, melon, spanner…	Hammer, penknife…	Key
4	The child cut paper with a pair of…	Shoes, glasses, bananas…	Hands, plyers…	Scissors, sheers
5	After months of practice, Lisa passed her driving…	Force, show, night…	Trial…	Test.
6	Simon ate his dinner with a knife and…	Nose, paper, pencil…	Spade, shovel, toothpick…	Fork, spoon

VERSION C				
	Item	**2 points**	**1 point**	**0 points**
1	Lisa went to the library to return some…	Rice, worm, umbrella…	Videos, DVDs…	Books, magazines
2	After her shower, she dried herself with a…	Sandpaper, box, lipstick…	Water, mop…	Towel, sheet.
3	He put a teabag in his mug and boiled the…	Petrol, spaghetti, orange juice…	Milk…	Kettle, water
4	He studied medicine to become a…	Plumber, engineer, carrot…	Researcher, nurse…	Doctor, psychiatrist, GP
5	The music started and everyone got up to…	Brush teeth, fly, cry…	Sit, sleep, shout, talk, yawn…	Dance, drink, go home
6	John picked up the leash and took his dog for a…	Step class, cremation, flight…	Bath, swim, drive, game of football…	Walk, run

Social Cognition – Part A

Instructions as in Version A.

Social Cognition – Part B: Score 0-12

Instructions as in Version A.

Memory – Delayed recall: Score 0-10

Instructions as in Version A.

Memory – Delayed recognition: Score 0-4

Instructions as in Version A.

Scores & Abnormality Cut Offs

The scores and cut-offs for abnormality are the same for all three versions of the ECAS. These are shown below.

			CUT OFF FOR ABNORMALITY
DOMAIN	SUBTESTS	MAX SCORE	≤ A, B, C
Language	*Naming, Comprehension, Spelling*	/28	26
Verbal Fluency	*Free Fluency (S,F,P), Restricted Fluency (T,D,M)*	/24	14
Executive	*Reverse Digit Span, Alternation, Sentence Completion, Social Cognition*	/48	33
	ALS-SPECIFIC:	**/100**	**77**
Memory	*Immediate recall, Delayed recall score, Delayed recognition*	*/24*	*13*
Visuospatial	*Dot Counting, Cube Counting, Number Location*	*/12*	*10*
	ALS NON-SPECIFIC:	**/36**	**24**
	ECAS TOTAL SCORE	**/136**	**105**

Appendix VI: Interview script for Chapter 6

SECTION A: ABOUT PARTICIPANT

"What is your area of speciality?"

Neurology	Psychology	Nursing	Other
☐	☐	☐	☐

If 'other,' please specify: _____

"For how many years have you worked in your area of speciality?"

Response:

"For how many years have you worked with MND patients?"

Response

SECTION B: SCREENING IN MND

Say: ***"I'm going to ask you about cognition and behaviour in patients with MND"***
"A screen is a brief test given to patients to see whether mental abilities, such as language and memory, or behaviours, are different to that of a healthy adult."
"I'm now going to ask you about screening for cognition in patients with MND"

"In your opinion, how important is it to screen for cognitive and behaviour change in patients with MND?"

Not important	Slightly important	Moderately important	Important	Very important
☐	☐	☐	☐	☐

"Why do you think cognitive and behavioural screening is/is not important?"

[RECORDED ANSWER]

"Do you think all patients diagnosed with MND should routinely be screened for cognitive and behavioural change?"

Yes	No
☐	☐

"What, if any, are the benefits to cognitive and behavioural screening in MND?"

[RECORDED ANSWER]

"In your practice, how frequently, if ever, do you screen for cognitive and/or behaviour change in MND?"

Never	Seldom	Sometimes	Often	Always
☐	☐	☐	☐	☐

"If never, Why?"
"Why do you screen as frequently as you do?"

[RECORDED ANSWER]

"What is the primary method by which you screen for cognitive or behavioural change?"

Formal Assessment	Clinical judgement	Other
☐	☐	☐

If 'other', please specify:

SECTION C: BARRIERS

Say: *"I would like to know your thoughts and opinions regarding potential barriers to cognitive and behavioural screening in MND.*

"What, if any, are the main barriers to screening for cognitive and behavioural change in MND?"

[RECORDED ANSWER]

"How might these barriers be overcome?"

[RECORDED ANSWER]

"*We're almost finished. Are there any other points or comments that you would like to make?"*

[RECORDED ANSWER]